



# **Exercise Haemodynamics: Physiology and Clinical Consequences.**

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A thesis submitted in fulfilment of the degree of Doctor of Philosophy

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## **Declarations by Author**

### **Originality**

This thesis contains no material which has been accepted for a degree or diploma by the University of Tasmania or any other institution, except by way of background information and of which is duly acknowledged in the thesis. To the best of my knowledge and belief, this thesis contains no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright. I have also acknowledged, where appropriate, the specific contributions made by co-authors of published and submitted manuscripts.

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### **Ethical Conduct**

All research associated with this thesis abides by the international and Australian codes on human and animal experimentation, and full ethical approval from the relevant institutions was obtained for all studies outlined in this thesis. All individual participants provided written informed consent for involvement in the respective research studies.

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### **Chapter 1**

**Schultz MG**, Sharman JE. Exercise hypertension: physiology and clinical consequences. *Manuscript in preparation*, August 2012.

#### **Author contributions:**

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### **Chapter 2**

**Schultz MG**, Otahal P, Cleland VJ, Blizzard CL, Marwick TH, Sharman JE. Exercise hypertension, cardiovascular events and mortality in healthy individuals: a systematic review and meta-analysis. *American Journal of Hypertension*. 2012. 26(3):357-366.

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### **Chapter 3**

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## **Chapter 6**

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The following papers are incorporated into chapters of this thesis and were either published or submitted for publication in peer reviewed scientific journals during the course of candidature.

### **Chapter 1**

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### **Chapter 2**

**Schultz MG**, Otahal P, Cleland V, Blizzard CL, Marwick TH, Sharman JE. Exercise hypertension, cardiovascular events and mortality in healthy individuals: a systematic review and meta-analysis. *American Journal of Hypertension*. 2012. 26(3):357-366.

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**Schultz MG**, Hare JL, Marwick TH, Stowasser M, Sharman JE. Masked hypertension is “unmasked” by low intensity exercise blood pressure. *Blood Pressure*. 2011. 20(5):284-9.

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### **Chapter 6**

**Schultz MG**, Davies JE, Hardikar A, Pitt S, Hughes AD, Sharman JE. Aortic reservoir pressure is related to volumetric aortic wall changes: a human physiological study. *Manuscript in final preparation*, July 2012.

### **Additional Publications That Do Not Form Part of the Thesis**

The following six publications or papers in submission for publication in peer reviewed scientific journals arose from candidature and whilst related, do not form part of the primary thesis.

**Schultz MG**, Gilroy D, Wright L, Bishop W LJ, Abhayaratna WP, Stowasser M, Sharman JE. Out-of-office blood pressure combined with central blood pressure for risk stratification. *European Journal of Clinical Investigation*. 2012. 42(4):393-401.

**Schultz MG**, Climie RED, Nikolic SB, Arhuja KD, Sharman JE. Reproducibility of cardiac output derived by impedance cardiography during postural changes and exercise. *Artery Research*. 2012, 6(2):78-84.

**Schultz MG**, Abhayaratna WP, Marwick TH, Sharman JE. Myocardial perfusion and the ‘J’ curve association between diastolic blood pressure and mortality. *American Journal of Hypertension*. 2013. 26(4):557-566.

**Schultz MG**, Climie RED, Nikolic SB, Arhuja KD, Sharman JE. The central hemodynamic response to postural stress is altered in patients with type 2 diabetes mellitus. *Journal of Human Hypertension*. [Epub ahead of print], December 2012.

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Climie RED, **Schultz MG**, Nikolic SB, Arhuja KD, Fell JW, Sharman JE Validity and Reliability of Central Blood Pressure Estimated by Upper Arm Oscillometric Cuff Pressure. *American Journal of Hypertension* 2012. 25(4):414-20.

Jones G, **Schultz MG**, Dore D. Physical activity and osteoarthritis of the knee: can MRI scans shed more light on this issue? *The Physician and Sports Medicine*, 2011. 39(3):55-61

### **Abstracts and Presentations at Scientific Conferences That Relate To This Thesis**

The following abstracts relate specifically to this thesis and were presented at national and/or international scientific conferences during the period of candidature.

**Schultz MG**, Davies JE, Black JA, Roberts-Thomson P, Hughes AD, Sharman JE. Elevation in central blood pressure during exercise is predominantly driven by forward-propagating waves: a first in man invasive exercise study. Second prize for best Young investigator oral presentation, Artery 12, Vienna, Austria, October 2012.

**Schultz MG**, Otahal P, Cleland V, Blizzard L, Marwick TH, Sharman, JE. A hypertensive response to exercise independently predicts cardiovascular events and mortality: a systematic review and meta-analysis. Poster presentation, Artery 12, Vienna, Austria October 2012.

**Schultz MG**, Davies JE, Black JA, Roberts-Thomson P, Sharman JE. Exercise hypertension is related to aortic reservoir function: a first in-human exercise central haemodynamic study. Oral presentation, ESSA conference, Gold Coast, April 2012.

**Schultz MG**, Otahal P, Cleland V, Blizzard L, Sharman, JE. Exercise hypertension predicts cardiovascular events and mortality in apparently healthy individuals: a systematic review and meta-analysis. Oral presentation, ESSA conference, Gold Coast, April 2012.

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**Schultz MG**, Otahal P, Cleland V, Blizzard L, Sharman, JE. A hypertensive response to exercise predicts cardiovascular events and mortality in apparently healthy individuals: a systematic review and meta-analysis. Poster presentation, HBPRCA Annual Scientific Meeting, Perth, December 2011.

**Schultz MG**, Hordern MD, Leano R, Coombes JS, Marwick TH, Sharman JE. One year of lifestyle intervention reduces the hypertensive response to exercise risk in patients with type 2 diabetes mellitus. Student finalist oral presentation, ESSA Conference, Gold Coast, April 2010.



**Schultz MG**, Hare JL, Marwick TH, Stowasser M, Sharman JE. Masked hypertension is “unmasked” by low intensity exercise blood pressure. Poster presentation, Artery 9, Cambridge, UK. September 2009.

**Schultz MG**, Hare JL, Marwick TH, Stowasser M, Sharman JE. Masked hypertension is “unmasked” by low intensity exercise blood pressure. Poster presentation, HBPRCA Annual Scientific Meeting, Sydney, December 2009.

**Dedication**

I dedicate this thesis to my wife Elizabeth for her loving friendship, unwavering support, patience and encouragement; and to my parents, Graeme and Dawn, who have always provided guidance and support through my education and life endeavours.

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## **Abstract**

High blood pressure (BP) is a leading risk factor for premature death relating to cardiovascular (CV) disease. Some individuals with normal resting BP may experience an excessive rise in BP with exercise; a condition termed ‘hypertensive response to exercise’ (HRE). Despite having normal resting BP, an HRE has been implicated in contributing to CV risk, but little is known on the condition. The broad aims of this research program were to determine; the prognostic and clinical significance of an HRE; the efficacy of a lifestyle intervention program to ‘treat’ an HRE and; the haemodynamic mechanisms contributing to exercise BP.

In study 1 (chapter 2), the prognostic value of an HRE for predicting CV events and mortality was examined via systematic review and meta-analysis on data from 12 studies (46,314 individuals). Elevated BP at moderate intensity exercise predicted CV events and mortality, independent of resting BP, age and multiple CV risk factors (HR=1.36, 95% CI: 1.02-1.83, P=0.039).

Study 2 (chapter 3) sought to determine a possible explanation as to why an HRE was associated with increased CV risk. In a cohort of 77 individuals with an HRE, a high prevalence (56%) of masked hypertension was observed. Moreover, moderate exercise systolic BP >190 mmHg revealed the presence of masked hypertension with high positive predictive value (94% sensitivity, P<0.001).

In study 3 (chapter 4), the effects of a one-year lifestyle (exercise and diet) intervention on exercise BP was examined in 185 individuals with type 2 diabetes mellitus. An HRE was not significantly reduced by the intervention. However, development of an HRE was preventable in those individuals without an HRE at baseline (P=0.020).

In study 4 (chapter 5), the haemodynamic mechanisms of exercise central BP were examined in 10 individuals undergoing coronary angiography. Exercise BP was principally related to increases in forward wave propagation generated by left-ventricular ejection, whereas mathematically-derived aortic reservoir function was unchanged with exercise. This mechanistic work was extended in study 5 (chapter 6), where aortic reservoir pressure was directly measured for the first time in 10 individuals undergoing coronary bypass surgery. Directly-measured and mathematically-derived aortic reservoir pressures were highly related, thus providing evidence for an ‘aortic reservoir function’ in generation of central BP.

In summary, this research shows that an HRE is related to increased CV risk, and this may be due to masked hypertension. Furthermore, it was possible to attenuate progression towards an HRE with lifestyle intervention. Finally, exercise BP was found to be predominantly due to forward wave transmission, and mathematically-derived aortic reservoir pressure is a valid construct relevant to understanding the physiology of central BP.

**Keywords**

Aorta

Blood pressure

Cardiovascular risk

Exercise physiology

Haemodynamics

Hypertension

Pathophysiology

Pulse wave analysis

Reservoir

Stress test

Wave intensity analysis

Wave reflection

## **List of abbreviations**

### **General**

CV – Cardiovascular

2D – Two dimensional

### **Haemodynamic**

24 ABPM – 24 hour ambulatory blood pressure (or monitoring)

AIx – Augmentation index

AP – Augmentation pressure

BP – Blood pressure

HRE – Hypertensive response to exercise

LV – Left ventricle (or ventricular)

LVMI – Left ventricular mass index

MH – Masked hypertension

PP – Pulse pressure

PWV – Pulse wave velocity

RWT – Relative wall thickness (left ventricular)

Tr – Pulse wave timing

WIA – Wave intensity analysis

### **Pharmacological**

ACEi – Angiotensin converting enzyme inhibitor

ARB – Angiotensin receptor blocker

### **Metabolic**

BMI – Body mass index

HbA<sub>1c</sub> - Glycated haemoglobin

HDL – High-density lipoprotein cholesterol

HOMR<sub>IR</sub> – Homeostasis model of insulin resistance

LDL – Low density lipoprotein cholesterol



**Statistical**

ANCOVA – Analysis of covariance

ANOVA – Analysis of variance

CI – Confidence interval

HR – Hazard ratio

n – Number of subjects

RR – Risk ratio

SD – Standard deviation

**Style Note**

There is an increasing convention to use the term “data” as a singular noun in scientific writing. The word “data” is however a plural noun, but is used extensively as a singular noun throughout this thesis.

## **Table of contents**

<b>Declarations by Author .....</b>	<b>i</b>
<b>Statement of Co-author Contributions to Papers Contained Within This Thesis.....</b>	<b>ii</b>
<b>Publications by the Author in Peer Reviewed Journals .....</b>	<b>v</b>
<b>Additional Publications That Do Not Form Part of the Thesis .....</b>	<b>vi</b>
<b>Abstracts and Presentations at Scientific Conferences That Relate To This Thesis .....</b>	<b>vii</b>
<b>Dedication .....</b>	<b>ix</b>
<b>Acknowledgements .....</b>	<b>x</b>
<b>Abstract.....</b>	<b>xii</b>
<b>Keywords .....</b>	<b>xiv</b>
<b>List of abbreviations .....</b>	<b>xv</b>
<b>Table of contents .....</b>	<b>xvii</b>
<b>List of Figures.....</b>	<b>xxi</b>
<b>List of Tables .....</b>	<b>xxiii</b>
<b>List of equations .....</b>	<b>xxiv</b>
<b>Preface.....</b>	<b>xxvi</b>
<b>Thesis Aims.....</b>	<b>xxviii</b>
<b>Chapter 1 – Exercise Haemodynamics: Reviewing the Physiology and Clinical Consequences.....</b>	<b>1</b>
1.1 Abstract .....	2
1.2 Overview .....	3

1.3 Exercise BP: the “normal” physiological response. ....	3
1.4 A hypertensive response to exercise. ....	3
1.5 The prognostic significance of an HRE .....	4
1.6 Explaining the increased CV risk associated with an HRE .....	6
1.7 Treatment of an HRE .....	7
1.8 Identifying the cause of an HRE. ....	8
1.9 Central haemodynamics and exercise .....	10
1.10 Summary .....	15

## **Chapter 2 – Establishing the prognostic value of a hypertensive response to exercise...17**

2.1 Abstract .....	18
2.2 Introduction .....	19
2.3 Methods.....	20
2.4 Results.....	22
2.5 Discussion .....	30
2.6 Conclusion. ....	32
2.7 Contribution of chapter 2 to the thesis aims. ....	33

## **Chapter 3 – Masked Hypertension may Explain the Increased Cardiovascular Risk Associated with a Hypertensive Response to Exercise. ....34**

3.1 Abstract .....	35
3.2 Introduction.....	36
3.3 Methods.....	36
3.4 Results.....	38
4.5 Discussion .....	44
3.6 Conclusion .....	46
3.7 Contribution of chapter 3 to thesis aims. ....	46

<b>Chapter 4 – Can a Hypertensive Response to Exercise be Modified by Lifestyle Intervention? .....</b>	<b>47</b>
4.1 Abstract.....	48
4.2 Introduction.....	49
4.3 Methods.....	49
4.4 Results.....	54
4.5 Discussion .....	60
4.6 Conclusion .....	62
4.7 Contribution of chapter 4 to the thesis aims .....	62
 <b>Chapter 5 – What are the Haemodynamic Factors that Determine Blood Pressure During Exercise? .....</b>	 <b>63</b>
5.1 Abstract.....	64
5.2 Introduction.....	65
5.3 Methods.....	65
5.4 Results.....	77
5.5 Discussion .....	86
5.6 Conclusion .....	89
5.7 Contribution of chapter 5 to thesis aims .....	90
 <b>Chapter 6 – Resolving the Physiology of Central Blood Pressure.....</b>	 <b>91</b>
6.1 Abstract.....	92
6.2 Introduction.....	93
6.3 Methods.....	94
6.4 Results.....	102
6.5 Discussion .....	113
6.6 Conclusion .....	115

6.7 Contribution of chapter 6 to thesis aims .....	116
<b>Chapter 7 – Conclusions and Future Directions .....</b>	<b>117</b>
<b>References .....</b>	<b>121</b>
<b>Appendices .....</b>	<b>139</b>
<b>Appendix 1 .....</b>	<b>140</b>
A1.1 Background .....	141
A1.2 Methods .....	141
A1.3 Results .....	141
A1.4 Conclusion .....	143

## List of Figures

Figure 1.1 Pulse pressure amplification.....	11
Figure 1.2 The central BP waveform.....	12
Figure 2.1 Literature search results.....	23
Figure 2.2 Categorical exercise blood pressure forest plots. ....	27
Figure 2.3 Continuous exercise blood pressure forest plots. ....	28
Figure 2.4. Funnel plots .....	29
Figure 3.1 The change in blood pressure during exercise .....	41
Figure 3.2 Light exercise blood pressure vs. ambulatory blood pressure.....	42
Figure 4.1. Participant selection and analysis.....	51
Figure 4.2 Change in hypertensive response status following intervention. ....	59
Figure 5.1 Data acquisition in the cardiac catheterisation laboratory.....	67
Figure 5.2 Combowire and its positioning within the ascending aorta.....	69
Figure 5.3 Screenshot from Combomap during haemodynamic data acquisition. ....	70
Figure 5.4. Example of signals output for calibration of pressure and flow velocity.....	71
Figure 5.5 Reservoir-excess pressure separation. ....	76
Figure 5.6 Wave intensity analysis at rest and during exercise. ....	81
Figure 5.7 Reservoir-excess pressure separation at rest and during exercise. ....	83
Figure 5.8 Change in forward compression wave intensity from rest to exercise vs. change in peak excess pressure from rest to exercise. ....	85
Figure 5.9 Change in systolic pressure from rest to exercise vs. change in reflection coefficient from rest to exercise.....	86
Figure 6.1 Measurement site in the ascending aorta.....	95
Figure 6.2 Calculation of aortic segment length. ....	98
Figure 6.3 Tracking the walls of the ascending aorta .....	99
Figure 6.4 Beat-to-beat reservoir-excess pressure separation.....	102
Figure 6.5 Overlaid aortic volume and reservoir-excess pressure variables.....	107

Figure 6.6 Normalised reservoir pressure and aortic volume. ....	108
Figure 6.7 Relationship between aortic volume and derived aortic reservoir function. ....	109
Figure 6.8 Relationship between aortic volume and aortic pressure. ....	110

## List of Tables

Table 2.1 Overview of studies included in the meta-analysis reporting exercise blood pressure and CV event and mortality outcomes.....	24
Table 3.1 Clinical characteristics of study population.....	39
Table 3.2 Haemodynamic differences between normotensives with an HRE and masked hypertensive individuals. ....	40
Table 3.3 Logistic regression model for predictors of masked hypertension.....	43
Table 4.1 Clinical and metabolic parameters of the study population at baseline and change over 12 months.....	55
Table 4.2 Resting blood pressure parameters between control and intervention groups at baseline and 12 months.....	57
Table 4.3 Post maximal exercise blood pressure parameters between control and intervention groups at baseline and 12 months. ....	58
Table 5.1 Origin and nature of waves described previously in the ascending aorta as defined by wave intensity analysis. ....	74
Table 5.2 Clinical characteristics of the study population.....	78
Table 5.3 Aortic haemodynamic parameters at rest and during exercise. ....	79
Table 5.4 Wave intensity analysis (WIA) and reservoir-excess pressures at rest and during exercise. ....	80
Table 6.1 Clinical characteristics of study participants. ....	103
Table 6.2 Haemodynamic and reservoir-excess pressure parameters at baseline. ....	105
Table 6.3 Wave intensity analysis and pressure wave separation at baseline: pre vs. post-reservoir subtraction.....	112



## List of equations

Equation 5.1 .....	73
Equation 5.2 .....	73
Equation 5.3 .....	73
Equation 5.4 .....	76
Equation 6.1 .....	101
Equation 6.2 .....	101
Equation 6.3 .....	101
Equation 6.4 .....	101

*“Every entity perseveres in its state of being at rest or of moving uniformly straight forward, except insofar as it is compelled to change its state by forces impressed.”*

**(Sir Isaac Newton).**

## **Preface**

High blood pressure (BP) or ‘hypertension’ is the number one modifiable risk factor associated with cardiovascular (CV) disease events and death. In 2003 the prevalence of hypertension in Australia was estimated at approximately 29% of the adult population; as common as 1 in every 3 older individuals.<sup>1</sup> The prevalence of hypertension is likely increasing as a direct result of an aging population and modern lifestyle practices. Hypertension is, therefore, a significant disease burden to Australian society. Pharmacological therapy, combined with dietary modification and regular physical activity may lower BP, but there remains a significant knowledge gap in the diagnosis, management and effective treatment of the condition. Whilst risk related to hypertension is traditionally assessed from brachial BP measured under resting conditions, recent research impetus is directed towards exploring alternatives (such as ambulatory, exercise and central BP) which may add considerable clinically relevant information to the overall assessment of CV risk associated with hypertension. Moreover, revisiting the fundamental physiology that underpins abnormal elevations in BP may also elucidate new information vital to the treatment of the condition.

Upon initiation of physical activity that elevates heart rate above resting levels, BP will normally increase. However, irrespective of normal BP at rest, during exercise, some individuals may experience an excessive increase in BP. This condition is termed a hypertensive response to exercise (HRE). An HRE contributes to an adverse CV risk profile, but there is little information regarding the pathophysiology of the condition. The first part of this thesis broadly explores the clinical significance of an HRE. More specifically, research was undertaken to 1) determine the potential prognostic value of an HRE; 2) determine a potential explanation for the increased CV risk associated with an HRE; and 3) determine the response of an HRE to treatment via exercise and lifestyle intervention.

The second part of this thesis aimed to resolve some of the fundamental physiological determinants of both resting and exercise BP. The focus of chapters 5 and 6 was on central BP, the pressure to which many of the most vital organs are directly exposed. Central BP predicts adverse CV outcomes independent of brachial BP, and, therefore, further resolution of the underlying haemodynamic contributions to central BP during exercise is required in order to fully understand the clinical importance of an HRE.

This thesis consists of a series of individual studies and resultant manuscripts prepared for publication in peer-reviewed scientific journals. Each chapter is a separate study in its own right, and is largely presented in its final published or submitted format. Only slight modifications to writing style and grammar, which do not alter the results and conclusions of the individual study have been made for clarity and consistency of presentation throughout the thesis. Where appropriate, additional figures concerning the methods of individual studies (chapters 5 and 6) or which highlight specific concepts (chapter 1) have been added to enhance overall comprehension. Each study contributes to the thesis aims, and this is specifically outlined at the end of each thesis chapter.

## **Thesis Aims**

### **Aim 1**

To establish whether a hypertensive response to exercise predicts cardiovascular events and mortality in healthy individuals undergoing exercise testing.

### **Aim 2**

To determine a potential explanation for the increased cardiovascular risk associated with a hypertensive response to exercise.

### **Aim 3**

To determine whether a hypertensive response to exercise can be reduced following one-year of exercise and lifestyle intervention in individuals with type 2 diabetes.

### **Aim 4**

To determine the haemodynamic mechanisms of exercise central blood pressure.

### **Aim 5**

To resolve the haemodynamic factors that contribute to resting and exercise central blood pressure.

# **Chapter 1 – Exercise Haemodynamics: Reviewing the Physiology and Clinical Consequences.**

## **1.1 Abstract**

Blood pressure (BP) will normally increase upon initiation of dynamic exercise. However, despite apparent normal BP at rest, some individuals will experience an excessive rise in BP with exercise, termed a ‘hypertensive response to exercise (HRE)’. An HRE is a relatively common condition in apparently healthy individuals, and is highly prevalent in those with type 2 diabetes mellitus. An HRE is a likely contributor to elevated cardiovascular (CV) risk, as it is associated with target organ damage and predicts the future development of hypertension, as well as CV events and mortality. Although somewhat speculative at present, research suggests that some of the CV risk associated with an HRE could be related to pre-existing, but ‘masked’ hypertension. Whilst an HRE may be amenable to treatment via pharmacological and lifestyle interventions, more work is required to determine the exact physiological cause. Nonetheless, an HRE is likely attributable to multiple factors, including large artery stiffness, increased peripheral resistance and metabolic irregularities such as insulin resistance and dyslipidaemia. Future research focus may be directed towards understanding the value of aortic or ‘central’ BP measured during exercise. Indeed, central BP independently predicts CV mortality at rest, and, therefore, a greater understanding of the underlying haemodynamic contributors to raised exercise central BP may have important clinical ramifications.

## **1.2 Overview**

Exercise stress testing is routinely performed to assess cardiovascular (CV) risk and reveal CV abnormalities (such as myocardial ischaemia and coronary artery disease) which are not always identifiable at rest. Each year in Australia alone, there are in excess of 400,000 exercise stress tests undertaken.<sup>2</sup> Measurement of brachial blood pressure (BP) is a fundamental component of the exercise stress test, generally measured at all incremental stages of a test.<sup>3</sup> Whilst abnormalities in exercise BP, such as a ‘hypertensive response to exercise’ (HRE) are common, and often reported to attending physicians, there may be little emphasis placed on the result. This is because at present, there is limited information with respect to the clinical usefulness, diagnosis and management of an HRE. This current review aims to bring together the available evidence, so as to highlight the potential clinical importance and underlying pathophysiological mechanisms that may contribute to exercise hypertension.

## **1.3 Exercise BP: the “normal” physiological response.**

Initiation of dynamic physical activity (such as running or cycling) increases the metabolic demands of the active musculature. Blood flow is directed away from non-active circulatory beds, and vasodilation of the arterioles supplying the active muscles may cause a reduction in systemic vascular resistance.<sup>4</sup> To offset the increased demand for oxygenated blood in active regions, cardiac output is boosted by an immediate increase in sympathetic activity, heart rate, optimisation of myocardial contractility (inotropy and lusitropy) and elevated venous return. The rise in cardiac output predominates over reduced vascular resistance, and mean arterial pressure becomes elevated.<sup>5</sup> Whilst diastolic BP remains largely unchanged, systolic BP will rise in a step-wise manner with increasing intensity of treadmill or cycle exercise,<sup>6</sup> theoretically reaching peak value at maximal exercise intensity. The change in BP with exercise, as well as the maximum systolic BP reached may differ considerably in healthy individuals depending on a number of factors, not limited to; age,<sup>7, 8</sup> gender,<sup>7</sup> resting BP,<sup>9</sup> fitness,<sup>8, 9</sup> body composition,<sup>8, 9</sup> seasonal variation,<sup>10, 11</sup> and alterations to any of the aforementioned acute physiological adaptations to exercise.

## **1.4 A hypertensive response to exercise.**

Irrespective of BP at rest, some individuals may experience an excessive rise in BP with exercise, a condition termed ‘hypertensive response to exercise’ (HRE). An HRE may occur



at any level of exercise intensity, including at submaximal exercise intensity, maximal exercise intensity or during the immediate recovery periods following exercise. Due to variation in definition of an HRE between studies, there is currently no consensus as to a specific 'threshold' value of exercise BP that constitutes an HRE. Despite this, an HRE is often outlined as an exercise systolic BP  $\geq$  the 90<sup>th</sup> percentile from age and gender specific normative data.<sup>7</sup> This reflects values of exercise systolic BP  $\geq$  210 mmHg for males and  $\geq$  190 mmHg for females, at any exercise workload. Several studies have somewhat confirmed the appropriateness of this definition of an HRE, owing to strong associations between exercise systolic BP above these values and increased CV risk.<sup>12-14</sup> Nevertheless, the incidence of an HRE varies widely according to its definition and the clinical characteristics of individual study populations. Prevalence of an HRE in normotensive cohorts is reported in the literature up to 40%.<sup>15, 16</sup> A more conservative estimate from a recent systematic review placed the prevalence of an HRE across all cohort studies to be at approximately 3 - 4% of individuals.<sup>17</sup> Interestingly, the prevalence of an HRE in those with type 2 diabetes mellitus (T2DM) may be substantially greater (reported in the order of >50%),<sup>18, 19</sup> possibly due to increased systolic BP reactivity to exercise.<sup>20</sup> Several studies have also reported that an HRE may be more likely in those with ambulatory or 'masked hypertension', with incidence ranging from 40 - 58%.<sup>21, 22</sup>

A clear distinction of an HRE should be made from the condition of exercise induced hypotension, which is the failure of BP to rise significantly with exercise (systolic BP increase <20 mmHg), or a drop in BP below that of resting levels during exercise. Exercise induced hypotension is potentially an equally important condition which is highly prevalent (up to 10% in patients with coronary artery disease),<sup>17</sup> and may be indicative of an aortic outflow obstruction, ventricular dysfunction or myocardial ischemia.<sup>23</sup> However, discussion of the clinical relevance and physiology of exercise induced hypotension is beyond the scope of this review, and focus is directed towards an HRE. In addition, although this thesis is related to the haemodynamic causes of an HRE, there may be a role of sympathetic activation in determining the BP response to exercise.

### **1.5 The prognostic significance of an HRE**

**Future incidence of hypertension.** Manolio et al. investigated the relationship between an HRE during treadmill testing and future incidence of hypertension in 3741 normotensive subjects.<sup>15</sup> After five years and adjustment for age, sex, resting systolic BP and other CV risk

factors, an HRE was associated with a 2.14 mmHg increase in resting systolic BP ( $P < 0.0001$ ). The authors speculate that this small increase in systolic BP over time may lead to increased incidence of hypertension and hypertension-related target organ damage. This suggestion was subsequently confirmed in the Framingham offspring study cohort,<sup>24</sup> and in a large Japanese normotensive population,<sup>25</sup> which highlight the independent association of an HRE with future incidence of hypertension. An HRE may also be an important risk factor for future essential hypertension in individuals with high-normal resting BP. Indeed, using a Cox proportional hazards survival model, Miyai et al. showed that after a mean follow-up period of 5.1 years, an HRE was independently associated with the risk of developing future hypertension after adjustment for traditional CV risk factors (risk ratio = 2.31, 95% CI = 1.45 - 6.25).<sup>26</sup>

**Relationship with Left ventricular structure and function.** Numerous cross-sectional studies have shown modest, but significant relationships between an HRE and left ventricular (LV) structure (hypertrophy, increased LV mass and relative wall thickness) in healthy individuals and those with borderline or essential hypertension.<sup>27-33</sup> In a large general population cohort of men and women from the Framingham Heart Study, high incidence (67%) of LV hypertrophy was found in individuals with an HRE (defined as exercise systolic BP  $\geq 210$  mmHg males,  $\geq 190$  mmHg females) with a 10% greater LV mass compared to those with a normal exercise BP response.<sup>34</sup> This is likely an important finding, given that structural alterations of the LV are the principal sign of target organ damage associated with hypertension, and may increase propensity to develop fatal arrhythmias.<sup>35</sup> However, in the study of Lauer et al.,<sup>34</sup> the relationship between LV structural abnormalities and an HRE became non-significant after adjustment for age, body mass and resting BP. Indeed, exercise BP may have no greater association with indexes of LV hypertrophy than that of BP measured at rest in individuals with hypertension.<sup>36</sup> Despite this, subtle indices of LV systolic dysfunction (impaired LV strain rate, peak systolic strain) were associated with an HRE in the study of Mottram et al., who suggested an HRE may likely represent early hypertensive heart disease.<sup>14</sup>

**Prediction of CV events and/or mortality.** The first report of a long term follow-up study within a large cohort of apparently healthy individuals found that systolic BP measured during moderate intensity cycle ergometry predicted both CV and all-cause mortality, independent of resting BP.<sup>37</sup> Numerous studies have since reported similar findings in healthy

cohorts, highlighting the potential independent prognostic importance of an HRE in the prediction of future adverse CV events (including cerebrovascular disease) and mortality.<sup>13, 16, 38-42</sup> These findings extend to BP measured during both moderate and maximal exercise workloads, although the effect of an HRE at maximal workloads on adverse outcomes is less clear.<sup>40, 42, 43</sup> Speculatively, this may be because measurement of BP during maximal exercise has a number of difficulties relating to noise and movement artefact. Studies have also indicated that exercise systolic BP does not carry incremental prognostic information over diastolic BP,<sup>44</sup> or after accounting for corresponding BP values at rest in individuals with hypertension.<sup>45</sup> Moreover, prospective studies in people with underlying CV pathologies, or in those with known or suspected coronary artery disease, an HRE has not consistently been implicated as contributing to increased mortality rates.<sup>12, 46-49</sup> Indeed, in these ‘higher risk’ patient cohorts, an HRE is often viewed as protective against adverse outcomes and may be indicative of maintenance of myocardial function. Again, given the wide variation in methods used and differential patient characteristics between studies, further clarification of the prognostic importance of an HRE is needed. *Chapter 2 of this thesis, via systematic review and meta-analysis of published literature, aims to resolve the uncertainty surrounding an HRE and the prediction of adverse CV events and mortality in apparently healthy individuals.*

## **1.6 Explaining the increased CV risk associated with an HRE**

Whilst an HRE is most likely clinically important, there is little understanding of why it is associated with increased CV risk. The current gold standard measurement of BP control is 24 hour ambulatory BP monitoring (24 ABPM).<sup>50</sup> This is because the use of 24 ABPM is additive in the prediction of CV mortality when combined with clinic BP.<sup>51</sup> It is possible that elevation of ambulatory BP is reflective of the BP exposure encountered in daily life activity and, therefore, more representative of the chronic burden of BP when compared with clinic BP. Many people may spend a significant proportion of each day moving (up to 35% standing and walking),<sup>52</sup> or in an ‘ambulatory’ state, perhaps akin to a moderate intensity of exercise. With this in mind, an HRE at a moderate intensity of exercise could be indicative of uncontrolled high BP. Indeed, subjects with an HRE likely have high-normal BP at rest, and record significantly higher ambulatory BP values compared to those with normal clinic BP.<sup>53</sup> Importantly, 24 ABPM identifies individuals with masked hypertension (MH, normal clinic BP and elevated ambulatory BP), a common BP condition that predicts CV disease mortality.<sup>51, 54</sup> Interestingly, studies have reported greater incidence of MH in individuals

with an HRE (up to 58 %).<sup>21, 22</sup> Furthermore, the study of Sharman et al. showed that in 72 untreated individuals with an HRE, MH was associated with increased LV mass and relative wall thickness, both of which are fundamental indicators of organ damage associated with hypertension.<sup>21</sup> It is therefore possible that MH may, at least in part, explain the increased CV risk associated with an HRE, which may be a marker of underlying hypertension. Despite this, the contribution of MH to the risk associated with an HRE remains largely speculative, and further work is needed to elucidate all causative factors. *The aim of Chapter 3 of this thesis is to explore whether raised systolic BP during moderate intensity cycle exercise can predict the presence of MH in a pilot study of individuals with an HRE.*

## **1.7 Treatment of an HRE**

**Pharmacological therapy.** Literature outlining the effect of modern pharmacological therapies on exercise BP is scarce. However, the effect of beta-blockade on exercise BP has been regularly studied and shown to significantly reduce exercise BP.<sup>55-57</sup> In a small cohort of patients with idiopathic hypertension, Lorimer et al. showed a 25% reduction in exercise systolic BP with 4 weeks active treatment with the beta-blocker metoprolol or combination metoprolol-hydrochlorothiazide.<sup>58</sup> In a similar study design, more modest reductions in exercise BP were induced with the use of sustained-release calcium channel blockers.<sup>59</sup> Such data may suggest a superior effect of beta-blockade in the reduction of exercise BP when compared with other antihypertensive medications. Indeed, Kokkinos et al. examined a cohort of 2318 men with hypertension and found that individuals undergoing beta-blocker based treatments were less likely to have an HRE (exercise systolic BP of  $\geq 210$  mm Hg) during routine exercise stress testing; a 68% lower risk when compared to other treatment regimens.<sup>60</sup> However, the duration of exercise testing and intensity of exercise reached by those on beta blockade treatment was less than those on other treatments. This may have reduced the maximum achievable systolic BP during exercise testing, potentially explaining the results of this particular study.

**Lifestyle intervention.** Lifestyle modification that includes regular exercise is universally regarded as important in the prevention and treatment of hypertension.<sup>23, 50, 61, 62</sup> There is clear evidence that aerobic exercise training results in a clinically significant reduction in resting BP.<sup>63, 64</sup> However, less information is available with respect to the potential effect of exercise training on exercise BP. It has been shown that those with a greater level of physical fitness may curtail BP reactivity to exercise stimuli when compared with less physically fit

individuals.<sup>8</sup> Moreover, lifestyle and exercise training interventions of varying type, frequency, duration and intensity should have an overall positive effect in reduction of exercise BP in healthy and patient cohorts.<sup>61</sup> The beneficial effects of exercise and lifestyle training on exercise BP may however be more readily evident in populations at greater risk related to high BP, such as those with essential hypertension, obesity or sedentary lifestyle.<sup>65-67</sup> Indeed, 16 weeks of progressive exercise training significantly reduced both maximal and submaximal exercise systolic and diastolic BP in a group of patients with severe hypertension.<sup>68</sup> In older and overweight adults, improved measures of general and regional body fat were also associated with lower exercise systolic BP following exercise training and dietary restriction.<sup>69, 70</sup> It is however currently unknown as to whether the development of an HRE can be attenuated, or regressed following exercise and lifestyle intervention. *To this aim, the effect of a one-year lifestyle (exercise and diet) intervention on exercise BP and the development of an HRE is examined in 185 individuals at elevated risk related to BP (those with T2DM) in chapter 4 of this thesis.*

## **1.8 Identifying the cause of an HRE.**

**Vascular function.** A failure of the vasculature to dilate appropriately in response to exercise may attenuate peripheral blood flow run off. This elevated resistance, combined with exercise induced increase in blood flow towards the periphery may result in an abnormally large increase in systolic BP with exercise. In contrast, appropriate vasodilation of the muscular arteries during exercise in healthy individuals will likely reduce pressure augmentation and decrease LV afterload.<sup>4</sup> Indeed, the clinical importance of appropriate vascular function during exercise was highlighted in the study of Fagard et al.<sup>43</sup> In this study of 143 hypertensive men, followed for 2186 patient years, systemic vascular resistance measured during exercise was the strongest predictor of future CV events, irrespective of BP at rest or during exercise.<sup>43</sup> Mechanistically, endothelium-dependent vasodilator dysfunction, assessed during reactive hyperaemia, could be a marker to denote an HRE.<sup>71</sup> Indeed, altered endothelial function may impair vasodilatory responses to exercise, increase vascular resistance and contribute to a large increase in systolic BP with exercise.<sup>72-74</sup> A decrease in nitric oxide levels under normal resting conditions may perturb endothelial function, resulting in a stiffening of the arterial network and relative increase in systolic BP.<sup>75, 76</sup> However, during exercise, the effect of nitric oxide on the appropriate regulation of vascular resistance, and thus exercise BP, is less clear.<sup>77-79</sup>

Despite this, systemic markers of vascular inflammation such as C-reactive protein (CRP) and interleukin-6 (IL-6) show moderate but significant associations with exercise systolic BP.<sup>80, 81</sup> It is therefore possible that such indices may be markers of underlying subclinical vascular irregularity associated with an HRE. In support of this notion, a cross-sectional study of 9073 middle aged healthy men found via multivariable logistic regression with adjustment for established CV risk factors, that those with an HRE (exercise systolic BP >210mmHg) had substantially increased risk of carotid atherosclerosis (HR=2.02, 95% CI=1.33-3.05) compared to individuals without an HRE.<sup>82</sup> Furthermore, albumin-creatinine ratio (a marker of likely vascular damage) has been associated in a cross-sectional analysis to elevations in exercise BP,<sup>83</sup> which may strengthen the potential link between an HRE and abnormal vascular function.

**Large artery stiffness.** With advancing age and disease, the compliance of the large arteries (namely the aorta) will decline.<sup>84</sup> At rest, large artery stiffness (as measured by aortic pulse wave velocity) is strongly associated with CV and all-cause morbidity and mortality and raised BP.<sup>84, 85</sup> Increased arterial stiffness is also a correlate of an HRE in individuals with essential hypertension.<sup>83</sup> Moreover, aortic pulse wave velocity and central pulse pressure (PP, as a surrogate of large artery stiffness) were recently found to be associated with submaximal exercise systolic BP in men and women of the Framingham offspring cohort study.<sup>74</sup> Physiologically, a reduction in aortic compliance could contribute to a decline in the buffering capacity of the vessel when faced with the exercise induced increase to LV outflow (cardiac output), and lead to an abnormal rise in systolic BP with exercise. Moreover, a progressive increase in the pressure exerted on the arterial wall of the aorta (such as which may be experienced with exercise) may lead to greater recruitment of collagen fibres, and an acute increase in stiffness of the vessel with exercise, resulting in an elevated systolic BP.<sup>86</sup> Exercise may also result in stiffening of the brachial artery, as a result of excessive arterial tone and vasoconstriction.<sup>87</sup> Taken all together, any stiffening of the large arteries will likely ensure a raised exercise BP. However, the properties of the large arteries may be of particular importance to the appropriate regulation of BP during exercise in individuals with T2DM. Whilst there is a high prevalence of an HRE in T2DM,<sup>18, 19</sup> there is also a strong association between insulin resistance and T2DM with large artery stiffness and abnormal elevations in exercise BP.<sup>88, 89</sup> Furthermore, individuals with insulin resistance and T2DM likely have

greater cardiac output at rest compared to healthy counterparts,<sup>90</sup> which again, combined with a stiff aorta may precipitate an abnormal rise in exercise systolic BP in these individuals.

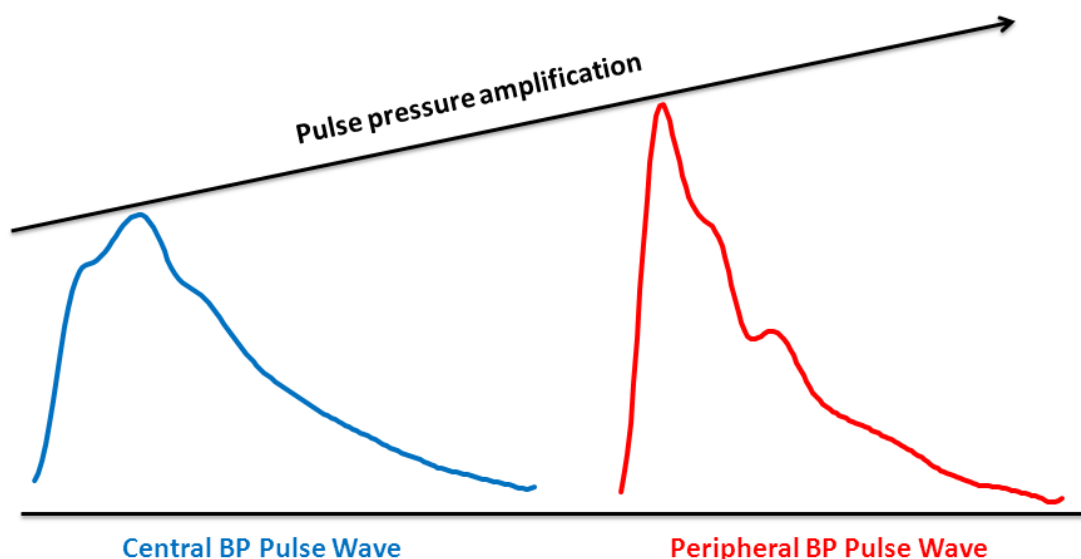
**Metabolic influences.** Hypercholesterolemia or dyslipidaemias may contribute to a poor CV risk profile via their relationship with vascular stiffening,<sup>91</sup> and may underlie elevations with BP during exercise. A recent study outlined a significant relationship between total cholesterol-to-high-density cholesterol ratio and submaximal exercise systolic BP.<sup>74</sup> Furthermore, a small study of healthy active men showed a moderate but significant relationship between serum cholesterol concentrations and the change in diastolic BP from rest to exercise ( $r>0.47$ ,  $P<0.0001$ ).<sup>89</sup> Interestingly, insulin resistance was also significantly associated with exercise diastolic BP changes, but there was no correlation between cholesterol or insulin resistance and exercise systolic BP in this study.<sup>89</sup> However, in 275 non-diabetic hypertensive patients, Park et al. showed that insulin resistance assessed by  $\text{HOMR}_{\text{IR}}$  (homeostasis model of insulin resistance) was significantly raised in those with an HRE, and  $\text{HOMR}_{\text{IR}}$  predicted the presence of an HRE independently of age, sex, body mass and baseline systolic BP (odds ratio=2.008,  $P<0.001$ ).<sup>92</sup> Moreover, insulin resistance was found to be independently associated with the systolic BP response to standardised exercise intensity in those with T2DM,<sup>93</sup> and insulin sensitivity may also play a role in the regulation of BP during exercise.<sup>94</sup> Taken together, a combination of metabolic irregularities including dyslipidaemia and insulin resistance could impair vascular reactivity,<sup>95</sup> increase vascular resistance and contribute to an abnormal increase in BP with exercise.

Despite the likely involvement of many CV and metabolic elements, research describing the potential underlying physiology of an HRE remains in its infancy and further work is required to elucidate all causative factors. However, most research to date has focused solely on brachial BP, neglecting potentially important information relevant to the understanding of an HRE that could be found with measurement of aortic or 'central' BP.

### **1.9 Central haemodynamics and exercise**

**Central BP.** Brachial BP is a potent predictor of CV and all-cause mortality.<sup>96</sup> Despite this, recent evidence suggests that central BP, the pressure to which the organs (heart, brain and kidneys) are directly exposed, predicts CV events independently of brachial BP.<sup>97</sup> It is understood that brachial systolic BP is not the same as central systolic BP, as the pressure pulse becomes amplified whilst propagating through the large central elastic arteries towards

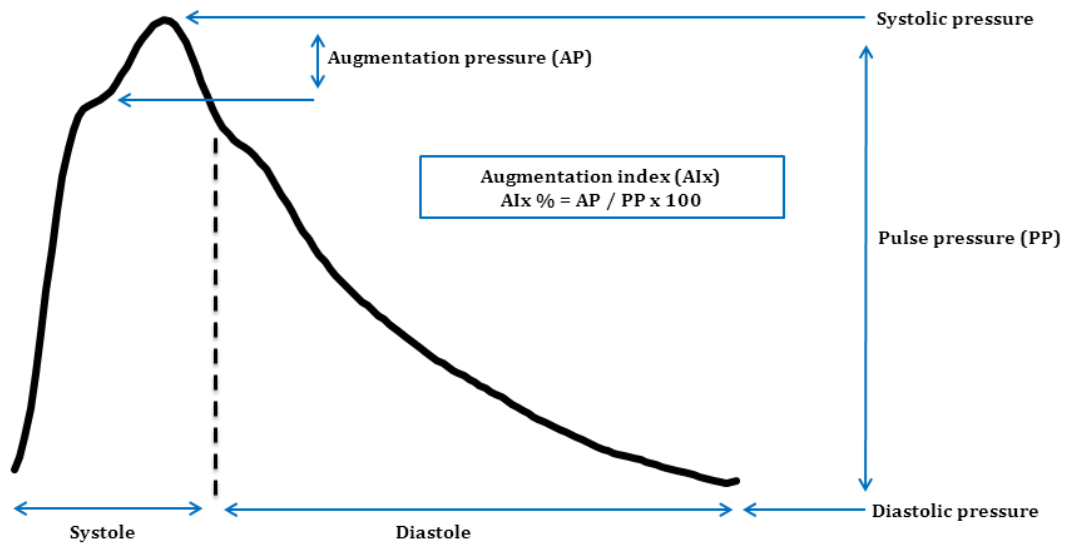
the smaller, more muscular arteries in the periphery (see Figure 1.1).<sup>98</sup> Indeed, central systolic BP is generally lower than brachial systolic BP, and may differ considerably (up to 30 mmHg) between individuals with similar brachial BP.<sup>99-101</sup> Central BP can be readily estimated via non-invasive measurement of the radial pulse, in a technique that is both valid and reproducible at rest and during exercise.<sup>6, 102-104</sup> Central BP parameters derived from this technique (such as pulse pressure, and augmentation index; see Figure 1.2) also predict adverse CV outcomes.<sup>97</sup> Whilst the clinical importance of central BP is largely known, resolution of the physiological determinants is required.



**Figure 1.1 Pulse pressure amplification**

This figure depicts the amplification of the systolic pressure pulse as it propagates away from the large central arteries near the heart (aorta) towards the muscular arteries located in the periphery. This increase in systolic pressure results in an amplification of the pulse pressure, and explains why central BP is usually lower than brachial BP.





**Figure 1.2 The central BP waveform**

Important prognostic parameters that are derived from the central BP waveform. This includes systolic pressure, the pulse pressure (systolic – diastolic BP) and augmentation index, which is calculated by expressing the augmentation pressure as a percentage of the pulse pressure.

**Wave reflection and central BP.** A long held explanation for the shape of the central BP waveform is based on wave reflection theory. With each cardiac ejection, a pressure wave is propagated forward through the arterial system. At sites of impedance mismatching such as major arterial bifurcations, some of the energy of this incident pressure wave is reflected back towards the heart. Upon meeting subsequent incident pressure waves, the reflected wave energy may augment the central BP waveform, raising systolic BP.<sup>98</sup> In young, healthy individuals, the reflected pressure wave is returned during diastole, which boosts coronary perfusion and minimises the augmentation of central BP and LV afterload. The progressive stiffening of the arteries that occurs with aging and disease,<sup>84</sup> (resulting in faster wave travel), may cause an early return of the reflected wave in systole, contributing unfavourably to LV afterload. However, application of this model implies that reflected waves are indeed returned progressively earlier (moving from diastole into systole) with augmentation of central BP that occurs with aging. A large meta-analysis has however indicated that there is no major shift in timing of reflected waves,<sup>105</sup> and augmentation of central BP should not be solely described by changes in reflected wave timing.<sup>106</sup>

Under the auspices of the wave reflection theory, the magnitude of wave reflection will also significantly contribute to augmentation of central BP, of which is inherently related to the magnitude of the incident pressure wave (increased incident wave pressure = increased reflected wave pressure), and arterial impedance properties.<sup>98</sup> However, in order to fit the model to physiological applications, the original definition of the wave reflection theory makes a number of assumptions relating to the CV system, downplaying the potential importance of the compliant properties of the arteries.<sup>107, 108</sup> It is therefore possible that by neglecting this physiological phenomenon, an unrealistic interpretation of central BP may be provided. Indeed, recent studies have indicated that reflected wave contribution to central BP is likely minimal, owing to the dispersion of reflected waves along the aorta, and entrapment of reflected waves in the periphery.<sup>109, 110</sup> This may suggest that capacitance or compliance of the aorta has a more influential role in determining central BP than originally conceived in wave reflection theory.

**Aortic reservoir function and central BP.** The reservoir-excess pressure paradigm is a hybrid physiological model that explains the shape of the central BP waveform whilst acknowledging the compliant properties of the arterial system.<sup>111</sup> The central BP waveform is derived as the sum of a reservoir pressure, which accounts for distension of the aorta during systole (to store blood) and elastic recoil throughout diastole (to release blood), combined with an excess or ‘wave’ pressure, which consists of discrete forward propagating and reflected pressure waves (see Figure 5.4 in chapter 5).<sup>112</sup> The reservoir pressure itself represents the minimum work the LV must perform in order to force blood into the aorta. The excess pressure is therefore the additional work required above this minimum.<sup>113</sup> Importantly, in order to properly quantify the effects of forward and reflected waves on central BP, it has been suggested that the ‘reservoir function’ must first be considered.<sup>114, 115</sup> Whilst the model does not discount the existence of reflected pressure waves, when considering the reservoir function of the aorta, the influence of reflected waves on augmentation of central BP is greatly reduced.<sup>116</sup> Despite this, recent criticism has been directed towards the reservoir-excess pressure paradigm upon suggestion that it may introduce error into haemodynamic analysis of central BP, causing spurious waves and altering ‘expected’ wave intensity profiles.<sup>117</sup> Irrespective, more work is required to determine the full clinical and physiological importance of the aortic reservoir pressure and its contribution to central BP. *In chapter 6 of this thesis, the first direct measurements of proximal aortic reservoir function are made under baseline conditions and in response to haemodynamic perturbation during cardiothoracic surgery. The direct measures of reservoir function are compared to the model derived reservoir pressure, in order to determine its true potential physiological relevance.*

**Exercise central BP.** The role of central BP during exercise has been seldom investigated. Early studies utilising intra-arterial measurement of BP in the aorta and radial arteries, indicated that central systolic BP may increase to a lesser extent than peripheral systolic BP during exercise.<sup>118, 119</sup> In other words, central to peripheral amplification of PP is raised during exercise when compared to the resting state. This may be due to the transmission characteristics of the brachial arterial vasculature, which, with increasing heart rate, show a frequency dependent signal increase, amplifying brachial pressure in relation to aortic pressure. This is likely of important clinical significance, given the independent prognostic value of raised central BP.<sup>97</sup> Non-invasive central BP synthesised from the radial pressure pulse has also revealed significant differences between peripheral and central

haemodynamics during exercise. Again, PP amplification is increased from rest to moderate intensity exercise in healthy individuals.<sup>120</sup> Moreover, Sharman et al. found that pulse pressure amplification is blunted (meaning increased central systolic BP relative to brachial systolic BP) during moderate intensity exercise in older individuals and those with hypercholesterolemia (individuals at elevated cardiovascular risk) when compared to healthy counterparts.<sup>121</sup> This was subsequently confirmed in another study which highlighted that older individuals have lower PP amplification during exercise compared with younger individuals.<sup>122</sup> In both studies the difference in PP amplification was not discernible at rest, which is an important observation because it suggests risk related to BP may be more evident from moderate intensity exercise central BP, rather than resting brachial BP. In an apparent anomaly, despite elevation of central BP with exercise, augmentation pressure (a marker of cardiac load, see Figure 1.2) may reduce with exercise in healthy individuals, likely owing to decreased peripheral resistance and elevated heart rate.<sup>98, 119-121</sup> Such changes in central haemodynamic load during exercise have been reconciled in frequency domain analysis by the contribution (or absence) of wave reflection, which is traditionally viewed as a surrogate marker of central BP augmentation.<sup>98, 123, 124</sup> Despite these contentions, a thorough examination of all the haemodynamic contributors to exercise central BP is lacking, and this may aid in determining the clinical relevance of raised exercise central BP. *With invasive measurement of aortic BP and flow velocity during cardiac catheterisation, a detailed description of the influence of both forward and reflected waves to augmentation of exercise central BP is given in chapter 5. For the first time, the reservoir-excess pressure model is applied in the setting of exercise, to determine the contribution of aortic reservoir function to exercise central BP.*

## 1.10 Summary

This review outlines the potential clinical importance of an HRE. In general, an HRE is a common condition associated with adverse CV outcomes, which includes target organ damage, the development of essential hypertension and future CV morbidity and mortality. Some of the CV risk attributable to an HRE may be due to a masked or ‘ambulatory’ hypertension, although further work is required to determine all factors involved. The potential mechanisms of an HRE are likely a manifestation of several CV anomalies including an altered metabolic profile and vascular dysfunction. Whilst exercise BP appears responsive to treatment via pharmacological and lifestyle modification, it remains unknown

as to whether an HRE can be prevented or regressed. Future research should be directed towards gaining further insight into the pathophysiological role of central BP during exercise, as this may likely add significant information to the clinical understanding of an HRE.

## Chapter 2

Establishing the prognostic value of a hypertensive response to exercise

Published in:

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**Schultz MG**, Otahal P, Cleland VJ, Blizzard CL, Marwick TH, Sharman JE. 2013. Exercise-induced hypertension, cardiovascular events, and mortality in patients undergoing exercise stress testing: a systematic review and meta-analysis.

*American Journal of Hypertension*, 26(3):357-66.

doi: 10.1093/ajh/hps053.

## Chapter 3

**Masked hypertension may explain the increased cardiovascular risk associated with a hypertensive response to exercise**

**Published in:**

<http://www.ncbi.nlm.nih.gov/pubmed/21449705>

**Schultz MG**, Hare JL, Marwick TH, Stowasser M, Sharman JE. 2011. Masked hypertension is “unmasked” by low intensity exercise blood pressure. *Blood Pressure*. 20(5):284-9.

doi: 10.3109/08037051.2011.566251

## Chapter 4

**Can a Hypertensive response to exercise be modified by lifestyle intervention?**

**Published in:**

<http://www.ncbi.nlm.nih.gov/pubmed/20881877>

**Schultz MG**, Hordern MD, Leano R, Coombes JS, Marwick TH, Sharman JE. 2011.  
Lifestyle change diminishes a hypertensive response to exercise in type 2  
diabetes. *Medicine and Science in Sports and Exercise*. 43:764-769.

doi: 10.1249/MSS.0b013e3181fcf034.



## Chapter 5

**What are the Haemodynamic factors that determine blood pressure during exercise?**

**Published in:**

<http://www.ncbi.nlm.nih.gov/pubmed/23716581>

**Schultz MG**, Davies JE, Roberts-Thomson P, Black JA, Hughes AD, Sharman JE. 2012. Exercise central blood pressure is predominantly driven by aortic forward travelling waves, not wave reflection. Accepted for publication, *Hypertension*, May 2012.

doi: 10.1161/HYPERTENSIONAHA.111.00584

## **Chapter 6 – Resolving the Physiology of Central Blood Pressure**

## 6.1 Abstract

Recent evidence highlights the important role of aortic reservoir pressure in determining central blood pressure (BP) morphology, although aortic reservoir function has never been measured. This study aimed to achieve this by measuring the cyclic change in aortic reservoir function (aortic volume). We hypothesised that directly measured aortic volume would be highly related to the mathematically-derived aortic reservoir pressure. Invasive pressure and Doppler flow velocity were recorded in the ascending aorta via intra-arterial wire in 10 male participants (aged  $62 \pm 12$  years) during coronary artery bypass surgery to derive aortic reservoir pressure. Simultaneous transesophageal echocardiography of the ascending aorta was undertaken to calculate the cyclic change in aortic volume. Using wave intensity analysis and pressure wave separation, dominant wave types throughout the cardiac cycle were identified (forward and backward, compression and decompression). Measures were recorded under baseline conditions and, in a sub-group ( $n=5$ ), following induced haemodynamic perturbation (head tilt or administration of Metaraminol). Following perturbation, diastolic BP increased (baseline  $55 \pm 8$  vs. perturbation  $58 \pm 5$  mmHg,  $P=0.046$ ) and there was a trend towards significant increase in peak derived reservoir pressure ( $73 \pm 8$  mmHg vs.  $77 \pm 7$ ,  $P=0.180$ ). Under all haemodynamic conditions, the directly measured aortic volume was strongly linearly related to derived reservoir pressure during systole (baseline  $r=0.980$ , perturbation  $r=0.960$ ,  $P<0.001$  respectively) and diastole (baseline  $r=0.987$ , perturbation  $r=0.840$ ,  $P<0.001$  respectively). Directly measured aortic volume and invasive aortic BP were qualitatively similar in morphology. Peak reflected pressure waves were reduced post-reservoir subtraction when compared with pre-reservoir subtraction state ( $4 \pm 3$  vs.  $2 \pm 2$  respectively,  $P=0.053$ ). We conclude that aortic reservoir function is an important physiological phenomenon that is related to the morphology of central BP.

## 6.2 Introduction

Central blood pressure (BP) is an independent predictor of cardiovascular (CV) events and all-cause mortality.<sup>97</sup> Fundamental to the physiological understanding of central BP is the study of arterial pressure wave morphology. A traditional explanation for the shape of the central BP wave describes pressure augmentation in terms of discrete incident and reflected wave transmission.<sup>98</sup> This provides a simple description of central BP shape, but does not account for the elastic properties of the proximal aorta, the most highly compliant segment of all large arteries. Notwithstanding, several studies have challenged the accepted viewpoint that elevations in central BP which occur with aging and disease are attributable to larger, and progressively earlier (within the cardiac cycle) return of reflected pressure waves.<sup>105</sup> There is also evidence to suggest that stiffening of the proximal aorta (such as that which occurs with aging) may decrease impedance mismatch at arterial bifurcations and effectively diminish the magnitude and return speed of reflected pressure waves in the aorta.<sup>160</sup> Adding to this, recent studies have concluded that the influence of discrete reflected waves on central BP may be minimal, owing to wave dispersion along the aorta and entrapment of reflected waves in the periphery.<sup>128,110</sup>

To this end, several investigators have outlined an alternate method to describe central BP which accounts for the elastic properties of the aorta (the reservoir function).<sup>111, 112, 115</sup> This hybrid model, known as the ‘reservoir-excess pressure’ theory, is based on the separation of the central BP waveform into a reservoir pressure, which represents the role of proximal aortic distension that occurs during systole (to store blood) and recoil during diastole (to release blood), and an excess or ‘wave’ pressure, composed of discrete forward and reflected pressure waves. Importantly, when accounting for the aortic reservoir pressure, the role of wave reflection in determining central BP is reduced. Indeed, augmentation of central BP may be largely attributable to elevations in incident pressure wave propagation and proximal aortic reservoir function,<sup>112, 116</sup> (see also chapter 5).

Despite these observations, the reservoir excess-pressure paradigm has attracted criticism due to findings from a modelling study in which consideration of the reservoir pressure introduced error into haemodynamic assessment of pressure wave travel (namely the overestimation of forward and backward expansion/decompression wave intensity).<sup>117, 161, 162</sup>

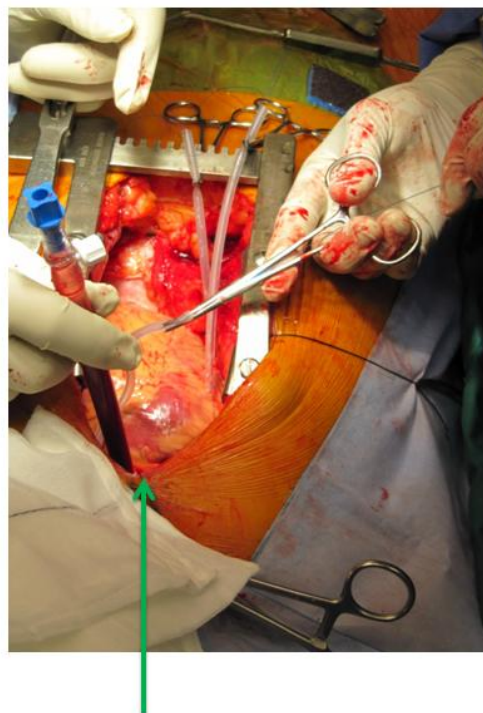
Some of the conjecture surrounding the reservoir-excess pressure paradigm may be because it is a mathematically derived construct. Indeed, the cyclic changes in reservoir function of the proximal aorta have never been directly measured and compared to the mathematically derived model of reservoir pressure. This was the aim of the current study, which we sought to assess by direct measurement of aortic reservoir function (cyclic aortic volumetric changes) under baseline conditions and also in response to haemodynamic perturbation. To our knowledge, this is the first study of its kind, and we hypothesised that there would be a strong relationship between derived and directly measured aortic reservoir function.

### **6.3 Methods**

**Study participants.** Twelve male patients scheduled to undergo coronary artery bypass surgery at the Royal Hobart Hospital, Hobart, Australia were recruited for participation in this study. Patients with aortic valve disease were excluded, due to the potential disturbance of normal proximal aortic haemodynamics. Power calculations were estimated on the basis of an expectation for a strong (near to equivalent) linear association between aortic volume and the derived aortic reservoir pressure. We determined that only 10 individuals were required to detect a conservative relationship of  $r=0.75$  with  $\alpha=0.05$ ,  $\beta=0.20$ . From the 12 patients consented to participate, data from two individuals was excluded due to technical difficulties encountered in the data acquisition phase.

**Study protocol.** Patients were prepared for coronary artery bypass surgery in accordance with standard clinical care. General anaesthesia was induced with fentanyl and midazolam, aiming for a mean arterial pressure (MAP) of 60-70 mmHg. Each patient was subsequently intubated and ventilated with a tidal volume of 7-8 ml/kg of body weight. Cardiothoracic surgeons performed a mid sternotomy, and the pericardium was opened to expose the ascending aorta. Prior to administration of cardioplegia and cannulation of the proximal aortic arch, the cardioplegia suture site was chosen as the point of maximum convexity of the ascending aorta, which usually coincided with its mid portion (in front of the right pulmonary artery). This cardioplegia purse string was used to pass a 21 gauge needle into the ascending aorta. Via this entry site, haemodynamic measurement of the ascending aortic pressure and flow velocity was made under baseline conditions (see Figure 6.1). In four patients a haemodynamic perturbation to increase BP and/or heart rate was induced by steep Trendelenberg position (10 degree head down tilt), and after a two minute stabilisation

period, the pressure and flow velocity measurements were repeated. In two patients, a haemodynamic perturbation was induced pharmacologically via administration of metaraminol, a potent alpha-adrenergic receptor agonist and sympathomimetic amine, which is routinely administered during cardiothoracic surgery to increase BP. During all haemodynamic measures, simultaneous transesophageal echocardiography of the proximal ascending aorta was performed to determine cyclic changes in aortic volume (as a direct measure of aortic reservoir function). Patient clinical characteristics were extracted from medical records. The study received ethical approval from the Tasmanian Human Research Ethics Committee, and all patients provided written informed consent prior to participation.



**Direct ascending aortic access**

#### **Figure 6.1 Measurement site in the ascending aorta**

This image depicts the direct entry site of the needle into the proximal ascending aorta, to which the Combwire was passed in order to acquire invasive aortic pressure and flow velocity measurements. The entry needle was inserted at the location of the aortic cannula (shown above), but all haemodynamic measurements were made prior to insertion of the cannula.

**Haemodynamic data acquisition.** Invasive aortic pressure and flow velocity was recorded in the proximal ascending aorta by intra-arterial pressure and Doppler flow velocity wire (single-use, 0.014", straight tip, Combwire, Volcano Therapeutic Corp, Rancho Cordova, CA, USA). Direct access to the ascending aorta was made via a 21g/4cm percutaneous entry thin wall needle (Cook Medical, Bloomington, IL, USA). The Combwire was advanced for a distance of 2 cm so that the tip remained in the ascending aorta. The catheter position was also confirmed on transesophageal echocardiography (when visible), and small movements of the Combwire were made in order to obtain optimal flow velocity and pressure traces. Digital conversion of the pressure and flow velocity analogue outputs was made using PowerLab ML870 8/30, (AD Instruments, Bella Vista, Australia) and recorded using LabChart 7 software (AD Instruments, Bella Vista, Australia). Data was acquired at the sampling rate of 1000 Hz and simultaneous three lead ECG recording was made to calculate heart rate. Calibration of the Combwire was made offline using a two point calibration method as previously described in chapter 5.

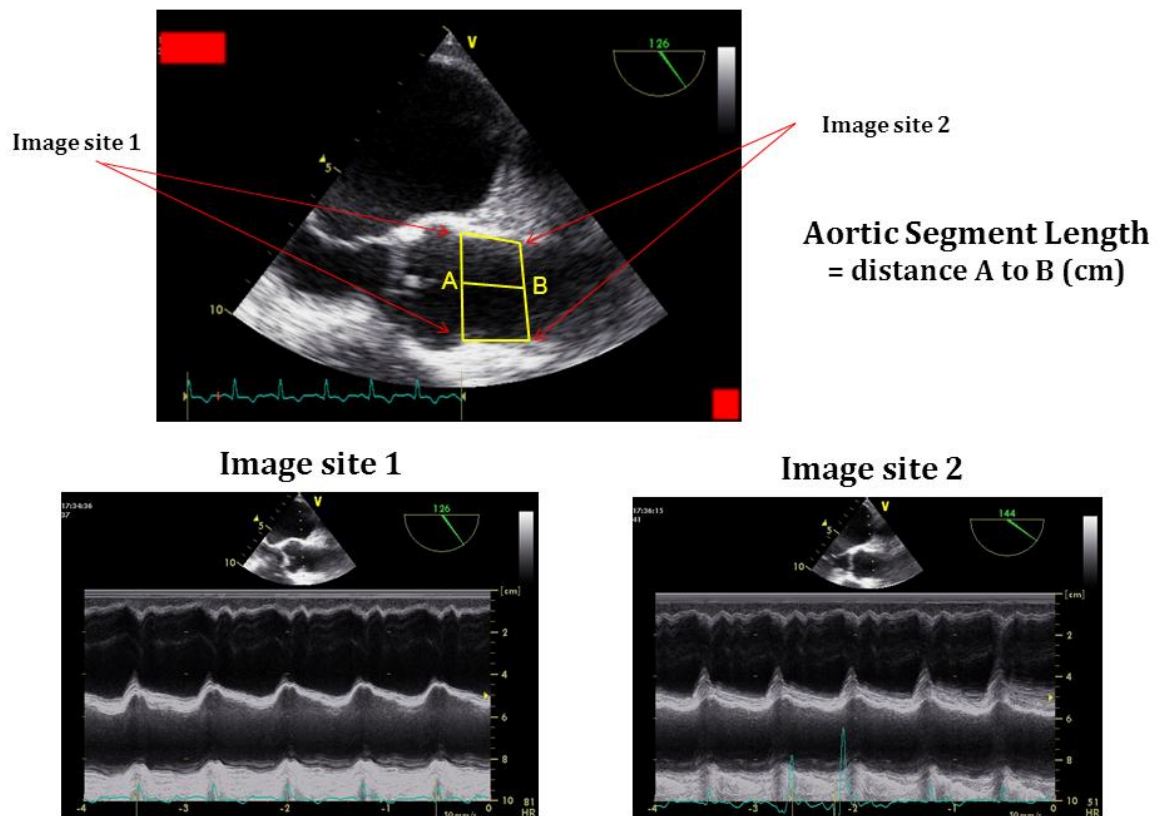
Aortic pressure and flow velocity traces, corresponding exactly to the capture period of each aortic image, were ensemble averaged offline for up to 6 heart cycles. Aortic systolic BP was defined as the maximum pressure point and diastolic BP was the minimum pressure point on the waveform. Aortic pulse pressure (PP) was defined as the difference between the systolic and diastolic BP. Augmentation pressure (AP, systolic BP – pressure at the first inflection point) was calculated using a Matlab written program. Augmentation index (AIx) was calculated from AP as a percentage of the overall PP. The sum of squares method was used to determine aortic wave speed, which has been previously outlined by Davies et al.<sup>152</sup>

**Echocardiography.** Images of the ascending aorta were captured using a General Electric ultrasound machine (Vivid i, GE Medical Systems, Milwaukee, WI, USA) with a 6T-RS (2.9 – 6.7 MHz) transesophageal echocardiography probe. The probe was inserted under general anaesthesia into the upper oesophagus for imaging of the proximal aorta (image site 1), before being retracted to image a more distal location along the ascending aorta (image site 2). For each imaging site, over several cardiac cycles (typically up to six beats), a long axis two dimensional image clip and m-mode image was acquired by imaging around the 120° plane, followed by the same images in short axis by imaging around the 30° plane. Appropriate gain, high frequency settings, narrow sector widths and minimum sector depths were used to optimise the image quality. Movement artefact was minimised by brief (<10

seconds) periods of apnoea when the patients oxygenation and ventilation safely permitted. Short and long axis m-mode images were saved in .mpeg and .bmp format for offline analysis. All imaging was performed simultaneously with haemodynamic measurement.

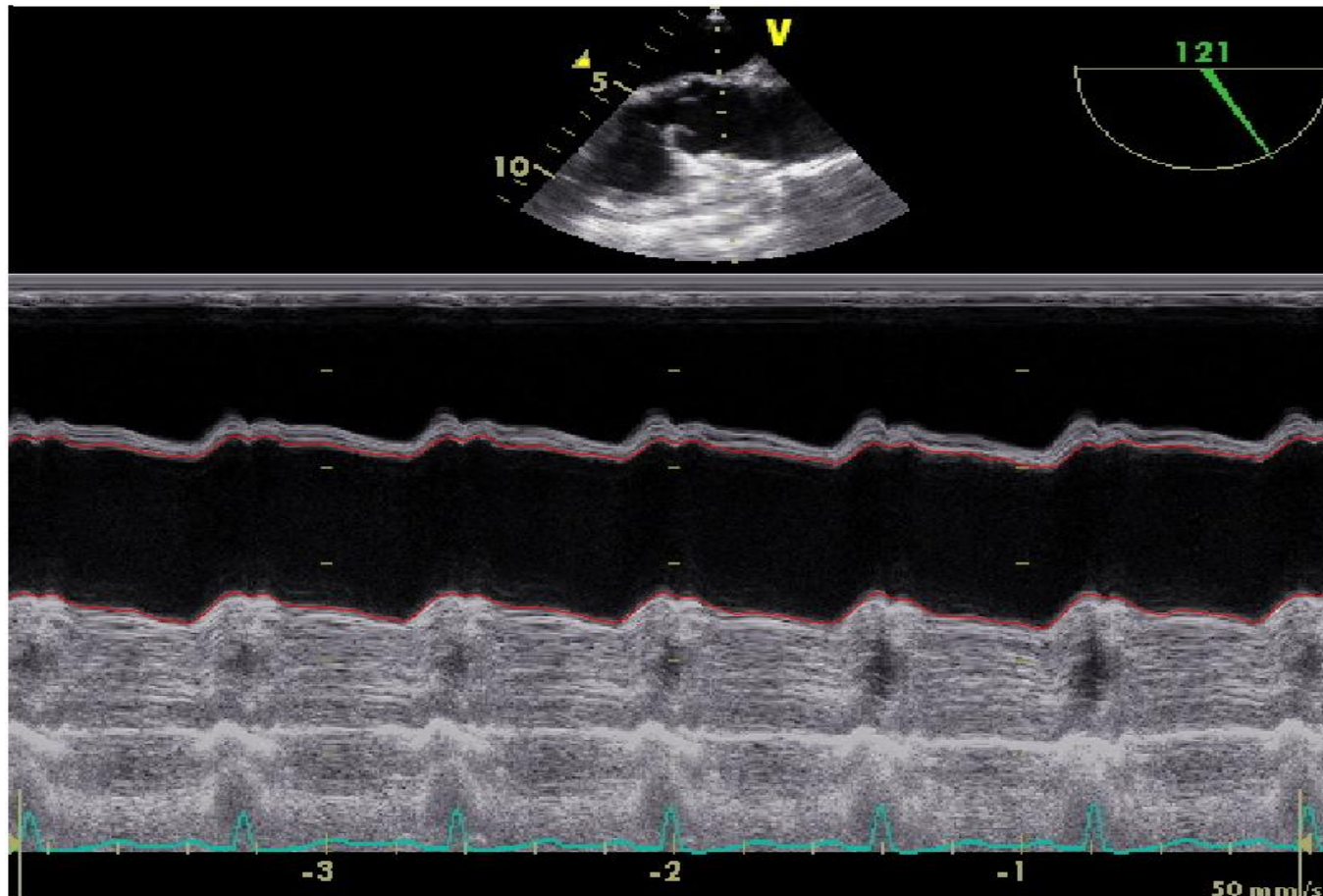
**Cyclic changes in aortic volume.** As a direct measure of aortic reservoir function, the cyclic changes in aortic volume were determined offline in a three step process. Firstly, measurement of the distance between the two echocardiography imaging sites (aortic segment length) was made. All segment length measures were performed on a two dimensional image, where both image capture sites were clearly visible. Accuracy of segment length measures was achieved by visualising landmarks relative to the capture sites on both long axis m-mode images, which were open at the time of all length measures. Repeat length measurements were made between the two imaging sites on the anterior wall, posterior wall and the central lumen. The average of the two central lumen measurements was treated as the aortic segment length (see Figure 6.2 for example). Secondly, the cyclic changes in aortic diameter were then calculated using a custom written, automated wall tracking algorithm. The best quality m-mode echocardiography image (short or long axis) was chosen to make all measurements of the cyclic changes in aortic diameter. An example of this diameter tracking is depicted in Figure 6.3. With both aortic diameter and segment length known, volume was calculated as:  $l\pi r^2$ ; where  $l$  was the aortic segment length between imaging sites 1 and 2; and  $r$ , was the aortic lumen radius. Under baseline conditions and following haemodynamic perturbation, a representative volumetric change waveform from one cardiac cycle was taken and combined between individuals to derive an average volumetric change waveform.





**Figure 6.2 Calculation of aortic segment length.**

Illustration of the process involved in determining aortic segment length. Both m-mode images are open (bottom) allowing visualisation of the two imaging sites along the proximal aorta. Length measurements were performed on the 2 dimensional image (top), where aortic segment length was calculated as the distance in the central lumen (A-B) between imaging sites 1 and 2.



**Figure 6.3 Tracking the walls of the ascending aorta**

Long axis m-mode echocardiography image of the ascending aorta. The red line is ‘tracking’ (via customised, automated tracking algorithm) both the posterior and anterior walls of the aorta over several cardiac cycles. This allowed determination of the cyclic changes in aortic lumen diameter (the difference between anterior and posterior wall), a necessary step in calculating the cyclic changes in aortic volume.

**Derivation of aortic reservoir pressure.** Aortic reservoir pressure accounts for the elastic energy stored in the aorta following distension of the vessel in systole, and the slow release of energy with recoil of the aorta during diastole. Aortic reservoir pressure ( $P_{\text{reservoir}}$ ) was derived from Equation 6.1, where  $P_{\infty}$  is the pressure asymptote at which flow through the microcirculation is negligible,  $P_d$  is the diastolic pressure at  $t = 0$ ,  $b = 1/RC$  where  $R$  is the resistance and  $C$  is the compliance property of the aortic reservoir. The time constant of the pressure decline throughout diastole is denoted by  $\alpha$ . The aortic excess pressure represents the pressure attributable to both forward and backward propagating waves, after subtraction of the aortic reservoir pressure from total pressure. Using a custom Matlab algorithm, separation of aortic pressure into both the reservoir and excess pressure components was performed on ensemble averaged aortic pressure (to obtain average values over the aortic imaging periods), and by using a continuous, beat-to-beat separation analysis (again over the aortic imaging periods) to allow beat matched comparison with the cyclic changes in aortic volume (see Figure 6.4 for example). The excess pressure was further divided into both forward and backward pressure components using equations 6.2 and 6.3, both pre-reservoir subtraction and post-reservoir subtraction. From this, a reflection coefficient was also calculated to assess magnitude of wave reflection, and was determined via the ratio of peak backward pressure to peak forward pressure and multiplied by 100 to obtain a percentage.

**Wave intensity analysis.** The interplay of both forward and reflected pressure waves in the aorta throughout the cardiac cycle was quantified using wave intensity analysis. As previously described,<sup>153, 155</sup> (see also chapter 5) waves can be classified from integration of aortic pressure and flow velocity based on 1) their origin and direction of travel (i.e. forward propagating waves that arise proximally as a result of LV ejection or reflected waves that originate in the periphery); and 2) their influence on pressure change across a wavefront (compression or decompression). The change in pressure is separated into forward ( $dP+$ ) and backward components ( $dP-$ ), using equations 6.2 and 6.3, where  $\rho$  is the estimated blood density ( $1050 \text{ kg.m}^{-3}$ ), and  $c$ , the wave speed derived from the single-point equation (Equation 6.4), where  $dP$  is the incremental change in BP, and  $dU$  the incremental change in blood velocity.

Wave intensity analysis was performed on ensemble averaged pressure and flow velocity waveforms that directly corresponded to each specific aortic imaging capture period, either without subtraction of the aortic reservoir pressure (pre-reservoir subtraction) or after subtraction of the aortic reservoir pressure (post-reservoir subtraction). The magnitude of wave reflection was also assessed via a wave reflection index, calculated as the ratio of peak backward compression wave to peak forward compression wave and multiplied by 100 to obtain a percentage value. Wave reflection index was calculated both pre-reservoir and post-reservoir subtraction.

**Equation 6.1**

$$P_{\text{reservoir}} - P_{\infty} = e^{-(a+b)t} \int_0^t [aP(t') + bP_{\infty}] e^{(a+b)t'} dt' + (P_d - P_{\infty}) e^{-(a+b)t}$$

**Equation 6.2**

$$dP_+ = \frac{1}{2}(dP + \rho c dU)$$

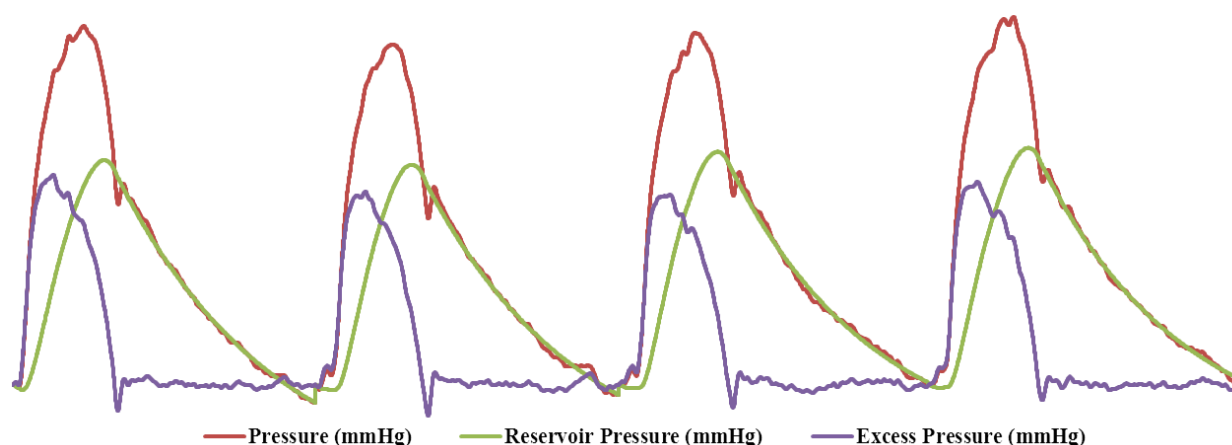
**Equation 6.3**

$$dP_- = \frac{1}{2}(dP - \rho c dU)$$

**Equation 6.4**

$$c = \frac{1}{\rho} \sqrt{\frac{\sum dP^2}{\sum dU^2}}$$

**Statistical analysis.** All statistical calculations were made using statistics software (PASW 18.0, SPSS Inc, Chicago, IL). Paired sample t-tests were used to compare the changes from baseline to perturbation in haemodynamic and pressure separated variables (including the directly measured aortic volume). Independent t-tests were used to compare wave intensity variables derived pre-reservoir and post-reservoir subtraction. Pearson correlation coefficients were calculated to assess linear relationships between variables.  $P < 0.05$  was considered statistically significant.



**Figure 6.4 Beat-to-beat reservoir-excess pressure separation**

Separation of the central pressure waveform (red) into aortic reservoir pressure (green) and excess pressure (purple) over several continuous cardiac cycles. This period of separation was performed at the same time as aortic imaging to allow alignment with the changes in aortic volume.

## 6.4 Results

**Clinical characteristics.** The clinical details of study participants are presented in Table 6.1. All patients were undergoing coronary bypass grafting and one patient was also having mitral valve repair. Most patients had hypertension and/or hyperlipidaemia, and all were taking pharmacological agents, including antihypertensive, lipid lowering, antiplatelet and aspirin medications. Three individuals had type 2 diabetes mellitus, of which two were receiving insulin therapy. There was a high prevalence of a cardiovascular disease family history, smoking history and three individuals had previous myocardial infarcts. Although two individuals had reduced LV ejection fraction ( $<50\%$ ), all patients were at the lower end of New York Heart Association (NYHA) functional classification. Data from one individual was excluded from analysis due to technical difficulty in appropriately tracking the aortic wall changes, leaving nine patients available for baseline analysis, five of whom also had measurements recorded following haemodynamic perturbation.

**Table 6.1. Clinical characteristics of study participants.**

<b>Variable</b>	<b>Mean <math>\pm</math> SD or n (%)</b>
Age (years)	62 $\pm$ 12
Height (cm)	175 $\pm$ 4
Weight (kg)	87 $\pm$ 12
Body mass index (kg/m <sup>2</sup> )	28 $\pm$ 5
NYHA functional classification 1	3 (30)
NYHA functional classification 2	6 (60)
NYHA functional classification 3	1 (10)
LVEF <50%	2 (20)
<i>Surgery performed</i>	
CABG x 1	1 (10)
CABG x 2	2 (20)
CABG x 3	4 (40)
CABG x 4	2 (20)
CABG x 5	1 (10)
Mitral valve repair	1 (10)
Previous myocardial infarction	3 (30)
Hypertension	9 (90)
Type 2 diabetes mellitus	3 (30)
Chronic kidney disease	1 (10)
Smoking history (no/former/current)	3 (30) / 5 (50) / 2 (20)
Family history of CVD	5 (50)
Hyperlipidaemia	8 (80)
<i>Pharmacological therapy</i>	
Lipid lowering	8 (80)
Aspirin	8 (80)
Calcium channel blocker	1 (10)
Beta blocker	5 (50)
Angiotensin converting enzyme inhibitor	4 (40)
Angiotensin receptor blocker	3 (30)
Antiplatelet	5 (50)
Diuretic	2 (20)
Digoxin	1 (10)
Insulin	2 (20)

N=10. NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass graft; CVD, cardiovascular disease.

**Haemodynamics at baseline and following perturbation.** All haemodynamic and derived reservoir-excess pressure variables measured at baseline are outlined in Table 6.2. Five of these individuals had a haemodynamic perturbation induced. Following perturbation, there was a significant increase in diastolic BP (baseline  $55 \pm 8$  vs. perturbation  $58 \pm 5$  mmHg,  $P=0.046$ ). All other haemodynamic variables, including heart rate ( $70 \pm 20$  vs.  $69 \pm 19$  bpm), systolic BP ( $85 \pm 9$  vs.  $93 \pm 17$  mmHg), MAP ( $65 \pm 6$  vs.  $69 \pm 6$  mmHg), central PP ( $30 \pm 10$  vs.  $35 \pm 20$  mmHg), AP ( $0 \pm 5$  vs.  $0 \pm 2$  mmHg), AIx ( $0 \pm 8$  vs.  $1 \pm 6$  %), aortic flow velocity ( $48 \pm 10$  vs.  $53 \pm 13$  cm/s) and aortic wave speed ( $6.2 \pm 1.2$  vs.  $7.5 \pm 2.4$  m/s) were not significantly altered after perturbation ( $P \geq 0.134$  for all). There was also no significant change in the reservoir-excess pressure separated variables, including peak reservoir pressure ( $73 \pm 8$  mmHg vs.  $77 \pm 7$ ,  $P=0.180$ ), integral reservoir pressure ( $8 \times 10^{-5} \pm 3 \times 10^{-5}$  vs.  $9 \times 10^{-5} \pm 4 \times 10^{-5}$  Pa.s,  $P=0.518$ ), peak excess pressure ( $68 \pm 6$  vs.  $74 \pm 11$  mmHg,  $P=0.164$ ) and integral excess pressure ( $6 \times 10^{-5} \pm 2 \times 10^{-5}$  vs.  $8 \times 10^{-5} \pm 5 \times 10^{-5}$  Pa.s,  $P=0.366$ ). Peak aortic volume did not significantly change following haemodynamic perturbation ( $16 \pm 10$  vs.  $20 \pm 16$  cm<sup>3</sup>,  $P=0.529$ ).

**Table 6.2 Haemodynamic and reservoir-excess pressure parameters at baseline.**

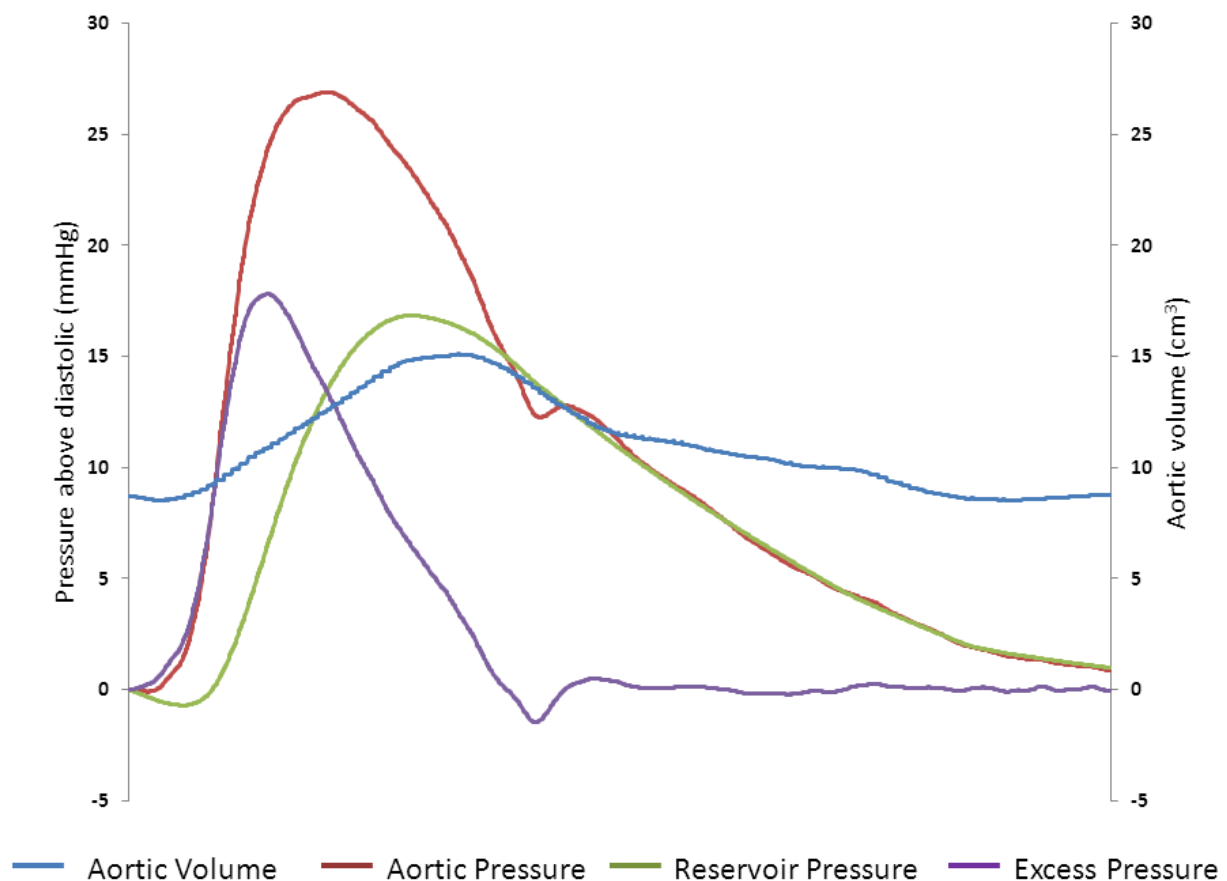
<b>Variable</b>	<b>Baseline (n=9)</b>
Aortic systolic pressure (mmHg)	$84 \pm 7$
Aortic diastolic pressure (mmHg)	$59 \pm 8$
Mean arterial pressure (mmHg)	$68 \pm 6$
Aortic pulse pressure (mmHg)	$25 \pm 9$
Augmentation pressure (mmHg)	$-1 \pm 2$
Augmentation index (%)	$-3 \pm 7$
Heart rate (bpm)	$75 \pm 16$
Peak aortic flow velocity (cm/s)	$52 \pm 12$
Aortic wave speed (m/s)	$5.3 \pm 1.5$
Peak derived aortic reservoir pressure (mmHg)	$75 \pm 8$
Integral aortic reservoir pressure (Pa.s)	$6 \times 10^5 \pm 3 \times 10^5$
Integral aortic excess pressure (Pa.s)	$5 \times 10^5 \pm 3 \times 10^5$
Peak aortic excess pressure (mmHg)	$68 \pm 5$
Peak aortic volume (cm <sup>3</sup> )	$17 \pm 9$

Data is mean  $\pm$  standard deviation.



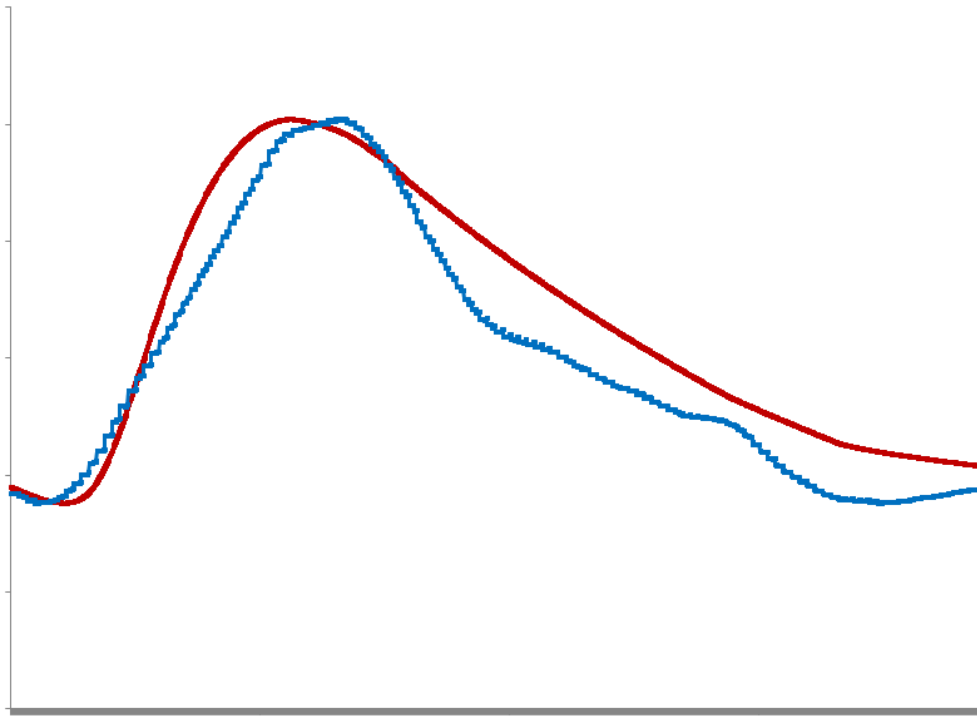
**Relationship between directly measured aortic volume, invasive aortic pressure and derived reservoir function.** Figure 6.5 depicts the relationship between directly measured aortic volume, invasive aortic pressure and derived reservoir and excess pressure across one cardiac cycle. The relationship between directly measured aortic volume and derived reservoir pressure appeared qualitatively linear and is more strikingly evident when derived reservoir pressure amplitude is normalised to the directly measured aortic volume (Figure 6.6). At baseline, directly measured aortic volume was significantly, and highly related to the derived reservoir pressure throughout systole and during diastole ( $r=0.980$ ,  $P<0.001$  and  $r=0.987$ ,  $P<0.001$  respectively, Figure 6.7A). Similarly, following perturbation, the relationship between directly measured aortic volume and derived reservoir pressure was strong during both systole ( $r=0.960$ ,  $P<0.001$ ) and diastole ( $r=0.840$ ,  $P<0.001$ , Figure 6.7B).

The relationship between directly measured aortic volume and invasive aortic pressure appeared as a somewhat ‘characteristic’ pressure-volume loop. Under baseline conditions (Figure 6.8A), at the beginning of the cardiac cycle there is a steep rise in invasive aortic pressure with a corresponding increase in directly measured aortic volume (although less steep) that continues until peak systole. From peak systole, invasive aortic pressure plateaus and then drops rapidly until aortic valve closure at end systole. At the same time, directly measured aortic volume appears to continue to rise until end systole. After closure of the aortic valve both invasive aortic pressure and directly measured aortic volume gradually return to baseline levels throughout diastole. Following haemodynamic perturbation (Figure 6.8B), the loop is qualitatively similar to baseline conditions, although there appears a much steeper and greater rise in invasive aortic pressure until peak systole. There is also a much steeper drop off in invasive aortic pressure during diastole. Overall, in response to perturbation, there is a rightwards shift in directly measured aortic volume at the onset of systole, as well as an increase in peak systolic pressure and volume.



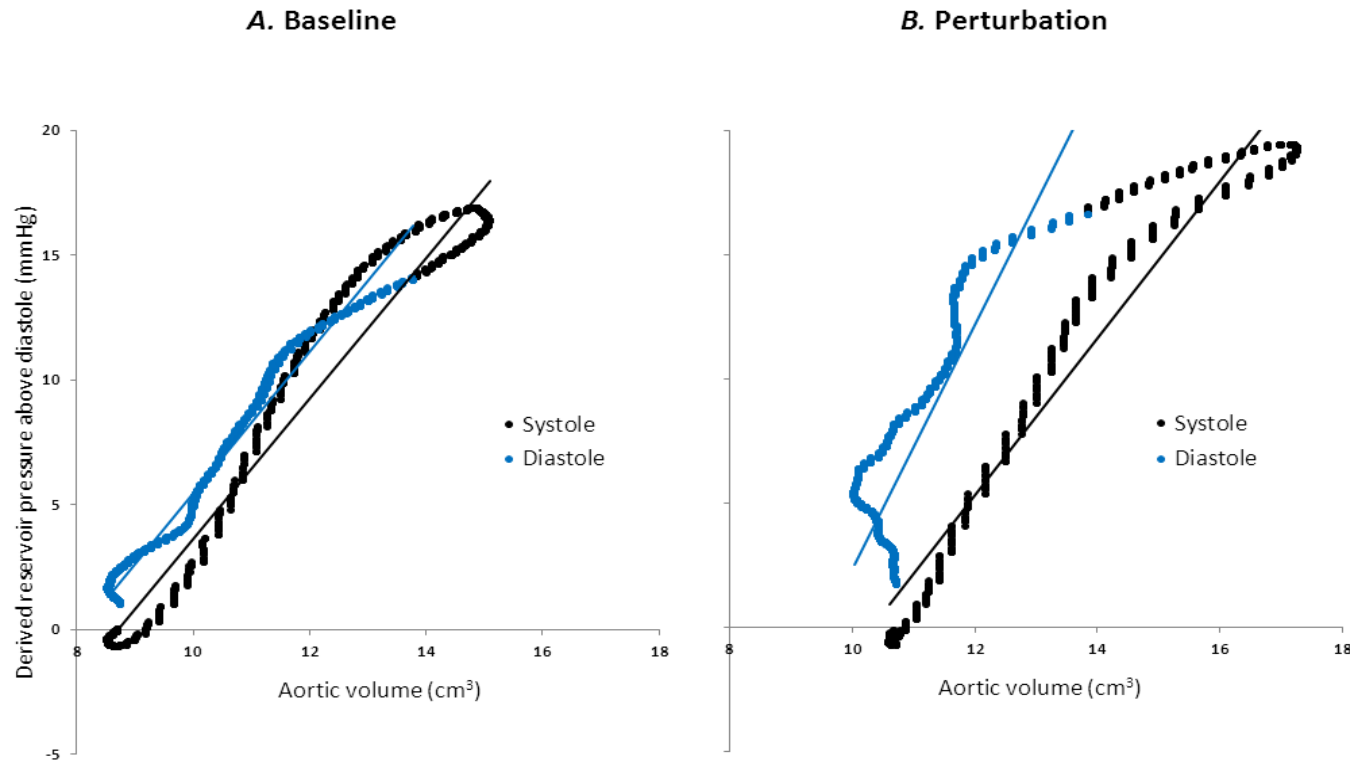
**Figure 6.5 Overlaid aortic volume and reservoir-excess pressure variables.**

Average of all baseline invasive aortic pressure waves (red) divided into reservoir (green) and excess pressure (purple) components over one cardiac cycle. The average directly measured aortic volume waveform (blue), representing a direct measure of aortic reservoir function, is also overlaid to depict its relationship to pressure and derived reservoir pressure parameters over one cardiac cycle.



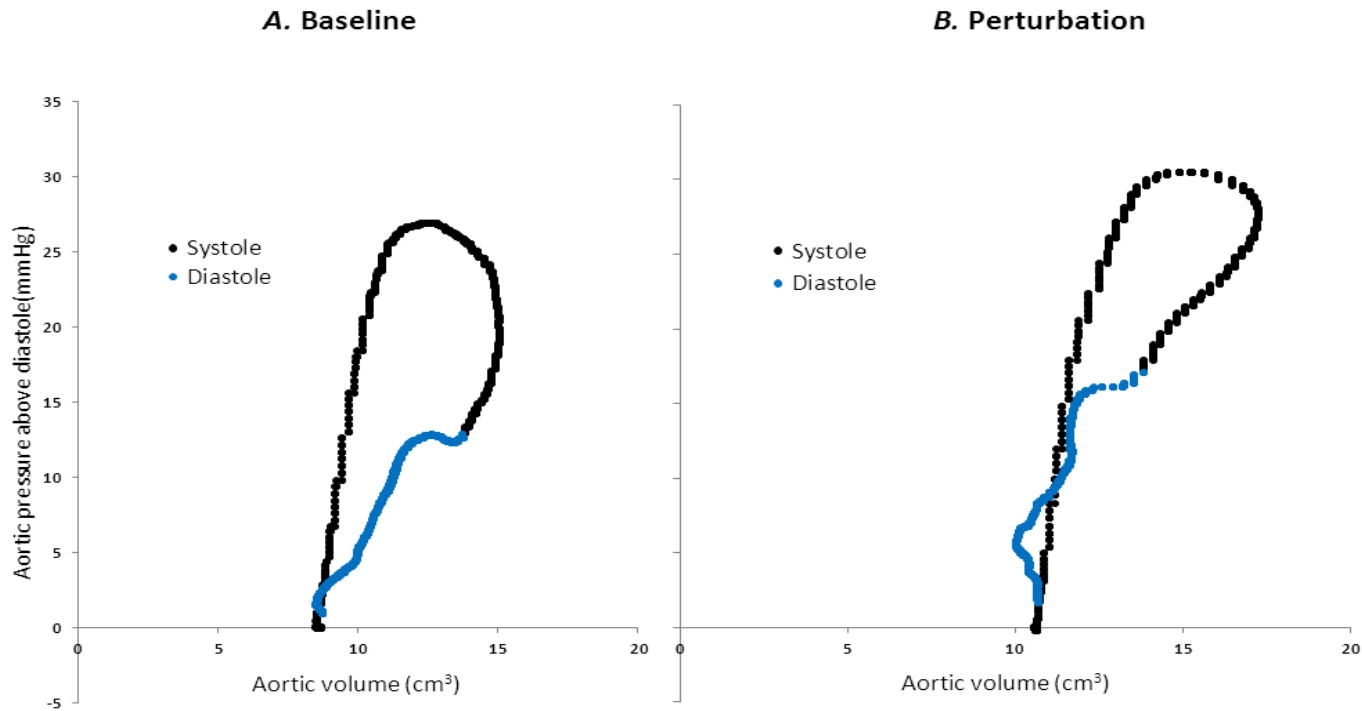
**Figure 6.6 Normalised reservoir pressure and aortic volume.**

This figure depicts estimated reservoir pressure (red waveform) normalised to the same relative amplitude as the directly measured aortic volume (blue waveform). Similarity is evident between the two waveforms. Due to normalisation, units are arbitrary.



**Figure 6.7 Relationship between aortic volume and derived aortic reservoir function.**

The relationship between aortic volume and derived reservoir pressure at baseline (a) and following haemodynamic perturbation (b), during systole (black markers) and diastole (blue markers). The solid black regression lines represents the significant linear relationship throughout systole (baseline  $r=0.980$ , perturbation  $r=0.960$ ,  $P<0.001$  for both) and the solid blue regression lines the significant linear relationship throughout diastole (baseline  $r=0.987$ ,  $r=0.840$  perturbation,  $P<0.001$  for both).



**Figure 6.8 Relationship between aortic volume and aortic pressure.**

The relationship between directly measured aortic volume and invasive aortic pressure at baseline (a) and following haemodynamic perturbation (b), presented during systole (black markers) and diastole (blue markers). Following haemodynamic perturbation, the relationship is qualitatively similar in appearance, albeit with a steeper rise and maximum pressure during systole, and steeper decline in pressure during diastole. The overall loop has also shifted to the right, indicating an overall increase in directly measured aortic volume following haemodynamic perturbation.

**Wave intensity analysis and pressure wave separation: pre-reservoir vs. post-reservoir subtraction.** Under baseline conditions (Table 6.3), there was a significant reduction in reflected pressure waves post-reservoir subtraction, and a trend towards a reduction in reflection coefficient (suggesting a reduction in reflected pressure waves relative to forward wave pressure) when compared to the pre-reservoir subtraction value. There was no significant reduction in forward pressure wave's post-reservoir subtraction. Wave intensity data is also depicted in Table 6.3. Under baseline conditions, we observed a trend towards a reduction in forward compression wave intensity post-reservoir subtraction, but this was not significant when compared to pre-reservoir subtraction values. There was no change in backward compression wave intensity (reflected wave pressure) or forward decompression wave intensity post-reservoir subtraction when compared to pre-reservoir subtraction. There was also no difference in wave reflection index between pre-reservoir and post-reservoir subtraction. In the five individuals who underwent measurements during haemodynamic perturbation, there was no significant difference between pre-reservoir and post-reservoir subtraction in forward compression wave intensity ( $24 \times 10^6 \pm 19 \times 10^6$  vs.  $18 \times 10^6 \pm 16 \times 10^6$  W.m<sup>-2</sup>s<sup>-1</sup>, P=0.676), backward compression wave intensity ( $-5 \times 10^6 \pm 5 \times 10^6$  vs.  $-3 \times 10^6 \pm 2 \times 10^6$  W.m<sup>-2</sup>s<sup>-1</sup>, P=0.441) or forward decompression wave intensity ( $7 \times 10^6 \pm 4 \times 10^6$  vs.  $9 \times 10^6 \pm 6 \times 10^6$  W.m<sup>-2</sup>s<sup>-1</sup>, P>0.711). There was also no significant difference between pre-reservoir and post-reservoir subtraction wave reflection index ( $27 \pm 10$  vs.  $21 \pm 10$  %, P=0.343) or reflection coefficient ( $19 \pm 18$  vs.  $13 \pm 18$  %, P=0.647).

**Table 6.3 Wave intensity analysis and pressure wave separation at baseline: pre vs. post-reservoir subtraction.**

Variable	Aortic WIA pre-reservoir subtraction	Aortic WIA post-reservoir subtraction	P value
Forward compression wave ( $\text{W.m}^{-2}\text{s}^{-1}$ )	$20 \times 10^6 \pm 6 \times 10^6$	$15 \times 10^6 \pm 7 \times 10^6$	0.139
Backward compression wave ( $\text{W.m}^{-2}\text{s}^{-1}$ )	$-2 \times 10^6 \pm 1 \times 10^6$	$-1 \times 10^6 \pm 1 \times 10^6$	0.334
Forward decompression wave ( $\text{W.m}^{-2}\text{s}^{-1}$ )	$5 \times 10^6 \pm 1 \times 10^6$	$6 \times 10^6 \pm 2 \times 10^6$	0.496
Wave reflection index (%)	$9 \pm 7$	$8 \pm 5$	0.569
Peak forward pressure (mmHg)	$47 \pm 10$	$44 \pm 11$	0.455
Peak reflected pressure (mmHg)	$4 \pm 3$	$2 \pm 2$	0.053
Reflection coefficient (%)	$10 \pm 7$	$6 \pm 5$	0.158

N=9. Data is mean and standard deviation. Wave intensity values are net wave intensity integrals (area under the curve). Reflection coefficient values presented were calculated using the ratio peak backward/peak forward pressure. Wave reflection index values were calculated using the ratio of peak backward compression wave intensity/peak forward compression wave intensity.

## 6.5 Discussion

This study represents the first direct measurement of the cyclic change in proximal aortic reservoir function. We found a strong linear relationship throughout both systole and diastole between the directly measured aortic reservoir function and the mathematically derived aortic reservoir pressure. Moreover, there was a trend towards reduction in reflected pressure wave contribution to central BP when reservoir function was considered. Importantly, these results enable interpretation of the aortic reservoir concept as a physiological phenomenon, and confirm the potential significance of aortic reservoir function to the understanding of central BP waveform morphology.

**Aortic reservoir function.** Under optimal conditions, the proximal ascending aorta has a compliant structure which functions to mitigate large cyclic fluctuations in aortic BP. During systole, LV contraction forces blood into the aorta and the vessel must expand to accommodate the increased volume of blood. Following closure of the aortic valve, the aorta recoils during diastole and blood is released into the more distal vasculature. This role in cushioning the rise in aortic pressure, is termed the ‘reservoir function’.<sup>112</sup> The reservoir function of the aorta has been quantified in the form of a mathematically modelled reservoir pressure, a construct which is theorised as representative of the work that the contracting LV must overcome in order to eject blood into the aorta. Indeed, the systolic portion of reservoir pressure is determined primarily by proximal aortic compliance (aortic stiffness)<sup>113</sup> and following LV ejection, the flow of blood into the aorta is briefly greater than the flow of blood out of the aorta. This results in distension of the vessel wall, which will increase aortic capacitance (volume) and elevate reservoir pressure.<sup>111</sup> However, until now, this reservoir function had not been confirmed as a physiological process occurring with each cardiac ejection in humans. In the current study, we observed this component of aortic reservoir function as a physiological phenomenon. Indeed, the instantaneous increase in directly measured aortic volume and derived aortic reservoir pressure shared a close linear relationship, both rising in a qualitatively similar manner throughout systole. Certainly, this relationship was not unexpected, because the measured increase in aortic volume should be proportional to the integral of the input flow rate, which is computed in the original derivation of the equation to estimate reservoir pressure as outlined by Wang et al.<sup>111</sup>



Of similar importance to the physiological understanding of aortic reservoir function is the discharge in reservoir pressure that ensues throughout diastole. Modelling studies have demonstrated that this decline in reservoir pressure may be inherently related to downstream arterial impedance.<sup>113</sup> However, decay of reservoir pressure during diastole is evident when applied to any vessel in the arterial system (i.e. the reservoir pressure waveform is qualitatively similar), and therefore thought to be predominantly determined by the more compliant properties of the proximal ascending aorta.<sup>112</sup> Although we did not measure peripheral arterial influences on the reservoir function, we observed a similar linear relationship between the directly measured aortic volume and derived aortic reservoir pressure during diastole. Indeed, both the aortic volumetric and reservoir waveforms slowly declined following aortic valve closure. Taken altogether over the full cardiac cycle, the strong linear relationships evident between directly measured aortic volume (as a direct measure of aortic reservoir function) and the mathematically derived aortic reservoir pressure, confirm the physiological nature of aortic reservoir function.

**The importance of reservoir function in determining central BP.** Central BP morphology has long been described in the frequency domain as emanating from discrete outgoing and reflected pressure waves. With each cardiac ejection, a forward propagating pressure wave is transmitted through the arteries towards the periphery. At sites of impedance mismatch (such as the aorta-iliac arterial bifurcation), part of this incident pressure wave is reflected back towards the heart resulting in augmentation of central BP if arriving during systole.<sup>98, 108</sup> Whilst generally accepted, this traditional explanation of central BP morphology fails to consider the compliant nature of the proximal aorta. However, based on the results of this study, the aortic reservoir function can now be considered a physiological phenomenon. Indeed, a large proportion of blood ejected with each cardiac contraction is dissipated within the elastic ascending aorta (up to 37%).<sup>163</sup> This highlights an important function, because when impaired (i.e. when aortic compliance is reduced), some of the pressure buffering capacity is lost.<sup>163</sup> An elevation in central BP may then ensue as a result of a more rapid increase in reservoir pressure for a similar rise in aortic volume.<sup>114, 163</sup> Indeed, appropriate aortic reservoir function is essential in order to minimise excessive rises in central BP and LV work. This has been demonstrated in animal studies whereby application of non-compliant grafts around, or in replacement of the proximal aorta acutely yields characteristically more

‘pathological’ aortic pressure waveforms, augmented pressure and increased myocardial load resulting in LV hypertrophy.<sup>164-166</sup>

Moreover, with advancing age (and disease) the compliant properties of human large arteries are progressively diminished.<sup>98, 167</sup> This results in a widening of PP and systolic BP becomes augmented. Traditional theory, which makes no account for aortic reservoir function, would attribute these pressure changes to an earlier return of, or increased magnitude of wave reflection.<sup>98</sup> However, there is now mounting evidence that wave reflection plays a less important role in determining central BP than originally conceived,<sup>105, 109, 110, 116</sup> (see also chapter 5). Indeed, there is no shift in reflected wave timing (moving from diastole into systole) that occurs with pressure augmentation associated with aging.<sup>105</sup> Adding to this, when considering the reservoir pressure, we showed an overall trend towards a reduction in reflected pressure waves (as evident from reduced peak reflected pressure and reflection coefficient). Importantly, these findings are in close alignment with previous literature that outlines reservoir pressure and forward pressure wave propagation as the more dominant contributors to central BP augmentation.<sup>116</sup> (see also chapter 5).

**Limitations.** Participants undergoing coronary artery bypass surgery in this study were of older age, under treatment with a number pharmacological agents, and with significant coronary disease. Moreover, as is routine in cardiac surgery, MAP was maintained at a relatively low pressure throughout the procedure. Therefore, the results of this study may not be further generalisable to other population groups and in circumstances where arterial pressure is greater. There was also significantly more variation in the relationship between aortic volume and derived reservoir pressure (particularly evident during diastole) in response to haemodynamic perturbations. Due to low study numbers, we chose to combine both the Trendelenberg and Metaraminol perturbations for analysis, and this may have limited our ability to demonstrate statistically significant differences in all variables from baseline conditions. Despite this a meaningful change in haemodynamics was still evident. Finally, although in this study we can confirm the physiological nature of aortic reservoir function, further studies are required to determine the clinical relevance of altered reservoir function.

## 6.6 Conclusion

This study highlights the physiological importance of proximal aortic reservoir pressure to the understanding of central BP. It confirms that the reservoir function of the aorta is a

physiological process occurring with each cardiac contraction. Moreover, the results add to a growing body of literature which suggests aortic reservoir pressure is fundamentally the most important constituent of central BP morphology. Further studies to determine the full clinical relevance of abnormal reservoir function are warranted.

### **6.7 Contribution of chapter 6 to thesis aims**

One of the limitations to the study outlined in chapter 5 of this thesis is that the reservoir pressure described is a theoretical, mathematical construct. Indeed, no direct measurement of the aortic reservoir function has ever been made in humans. The results of chapter 6 represent the first direct measurement of the cyclic changes in aortic reservoir function. Importantly, it has been demonstrated that the derived aortic reservoir pressure is highly related to the directly measured reservoir function of the aorta. These results enable interpretation of the aortic reservoir function as a physiological phenomenon, confirming the importance of aortic reservoir pressure to the understanding of central BP morphology.

## **Chapter 7 – Conclusions and Future Directions**

This thesis broadly confirms that a hypertensive response to exercise (HRE) is a clinically important entity. It is shown that an HRE holds independent prognostic value (chapter 2), that the risk associated with an HRE may be related to masked hypertension (MH, chapter 3), and that the development of an HRE can be effectively slowed via exercise and lifestyle intervention in individuals at heightened cardiovascular (CV) risk (chapter 4). Moreover, this thesis describes the underlying haemodynamic contributors to exercise central BP (chapter 5), which largely consist of forward wave propagation and aortic reservoir function. The importance of aortic reservoir function to the understanding of central BP was also confirmed via direct measurement in the aorta for the first time in humans (chapter 6). Taken altogether, this thesis provides novel information, and represents a significant advancement to the understanding of the physiology and clinical consequences of an HRE.

The results of chapter 2 represent one of the first comprehensive reviews of the literature and calculation of pooled risk estimates on the prognostic utility of an HRE. The results specifically outline that an HRE independently predicts CV events and mortality in healthy individuals undergoing exercise stress testing. Of particular note, an HRE was most strongly associated with CV events and mortality at a moderate intensity of exercise when compared with maximal exercise intensity. A logical next step is to retrieve the raw data from each individual study in order to perform further analysis and determine specific cut point values of exercise systolic BP which denote an HRE at specific exercise intensities (moderate and maximal). This may serve to inform clinicians supervising exercise stress testing of a threshold in which an HRE is likely indicative of elevated CV risk related to high BP. Further studies should also examine the prognostic relevance of an HRE in other population groups, such as those with coronary artery disease and type 2 diabetes (T2DM). Furthermore, synthesis of information regarding the prognostic value of an HRE to predict future incidence of essential hypertension is also needed.

The results of chapter 3 describe a potential explanation for some the increased CV risk associated with an HRE. Indeed, MH is highly prevalent in individuals with an HRE, and can be readily identified via measurement of BP during moderate intensity exercise. The results outline a potentially important link between raised ambulatory BP and an HRE, and, speculatively, given that individuals with an HRE in this study had ‘high normal’ BP at rest, an HRE could be indicative of a pre-hypertensive state. Despite this, these findings were confined to a small population of individuals with an HRE, and further verification, in larger

sample groups and in those without an HRE is needed. To this end, following on from the work in this thesis, a large prospective study aimed at determining the relationship between an HRE and MH is underway (the 'UNMASKED' BP study). In this study, more than 700 individuals will undergo BP measures during exercise stress testing and they will also have 24 ABPM recorded. It is expected that there will be a large number of individuals with both an HRE and MH, thus confirming that MH may explain the underlying CV risk of an HRE as alluded to in chapter 3. Additionally, a comprehensive haemodynamic assessment (eg. cardiac output, peripheral vascular resistance, central BP and large artery stiffness) is being undertaken in a sub-group of individuals (n=80 with an HRE and n=40 without an HRE) to determine the physiological mechanisms responsible for an HRE and its relationship to MH.

The prevalence of an HRE is significantly greater in those with T2DM, adding to the already substantial CV risk profile associated with the condition. In chapter 4, the usefulness of a one-year exercise and lifestyle intervention to 'treat' an HRE was examined in a population of individuals with T2DM. The results show that one-year of lifestyle intervention can significantly improve metabolic profile, increase functional capacity and, importantly, attenuate the development of an HRE in patients with T2DM. It does however remain unknown as to whether regression of an HRE, via improvements to cardiac structure may occur with longer duration, and more physically intense exercise and lifestyle interventions. Indeed, further studies are required to determine this, and to fully elucidate the role that exercise and lifestyle change may have in prevention and treatment of an HRE in other patient cohorts. Moreover, given the heightened CV risk of an HRE associated with T2DM, further studies are required to determine the underlying physiological mechanisms of an HRE in this patient group. Again, this is being pursued in the UNMASKED BP study, where in addition to the substantial battery of haemodynamic measures, potential metabolomic markers of an HRE are being identified for the first time.

Chapter 5 makes an important contribution to the haemodynamic understanding of both resting and exercise central BP. Whilst current theory would ascribe augmentation of central BP to increased magnitude of arterial wave reflections, the results of this study outline a less crucial role. Indeed, during exercise, wave reflection remains largely unchanged, and central BP is augmented predominantly by elevations in incident pressure waves originating from LV ejection. Moreover, separation of the exercise central BP waveform into the so called 'reservoir' and excess pressure components provides novel mechanistic insight into central

BP changes with exercise, which cannot be explained by traditional wave reflection theory. Again, given the elevated CV risk associated with an HRE, the results of chapter 5 could have important clinical implications. Future studies may direct attention towards establishing the clinical and prognostic value of exercise central BP to predict adverse CV outcomes as this currently remains unknown. Some evidence to suggest a clinically important role for moderate intensity exercise central BP may soon be revealed from analysis of data from the BP GUIDE study, in which we aim to determine the prognostic value of moderate intensity exercise central BP for predicting the change in cardiac size over one year in patients with controlled essential hypertension. Furthermore, with the advent of new devices that may enable accurate measurement of 24 hour ambulatory central BP, a prospective study, with hard endpoints (such as cardiovascular events and/or mortality), may enable determination of the true clinical relevance of moderate exercise and ambulatory central BP.

Chapter 6 represents the first direct measurements of the cyclic changes in aortic reservoir pressure. The results show that the mathematically derived aortic reservoir pressure is inherently related to the directly measured reservoir function of the aorta. This implies that due acknowledgement of the cyclic changes in aortic distension and recoil (the reservoir function) is required in order to understand the haemodynamic contributions to central BP. Despite this, the full clinical relevance of aortic reservoir function is unknown. Further development of non-invasive techniques (such as echocardiography) to effectively and rapidly measure the reservoir function of the aorta, both at rest and during exercise, may enable wider clinical application. Once achieved, this will likely facilitate a large scale prospective study to definitively determine the clinical implications of a raised or abnormal aortic reservoir pressure.

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## **Appendices**

## **Appendix 1**

Appendix 1 represents information and data analysis that was originally completed for the manuscript contained within chapter 3 of this thesis. The data involved with central BP and pulse wave analysis variables was removed from the published manuscript at the request of peer reviewers at the time of publication, but is presented here as it was originally presented in the manuscript prior to removal.

### **A1.1 Background**

Estimation of central BP from the pulse waveform recorded non-invasively at the radial or carotid arteries has been shown to provide clinically important information beyond that derived from brachial BP.<sup>84, 99</sup> It is however unknown if central BP or other pulse wave parameters such augmentation index (AIx), measured during exercise, may identify patients with masked hypertension (MH). This was an additional aim of the study presented in chapter 3 of this thesis.

### **A1.2 Methods**

**Pulse wave analysis.** Hand-held (resting) and servo-controlled (exercise) radial applanation tonometry (Colin CBM-7000; Colin Corp., Komaki City, Japan) were used to obtain peripheral pressure waveforms from the dominant arm. Pulse wave analysis (SphygmoCor 7.1; AtCor Medical., Sydney, Australia) was then used to synthesise aortic pressure waveforms (and central BP) from the radial waveform using a generalised transfer function shown to be valid and reproducible<sup>6, 103</sup> during light exercise. All radial waveforms were calibrated with the brachial BP values acquired at the same time (within  $\approx 1$  minute). Central Pulse pressure (PP) was calculated as the difference between central diastolic BP and Systolic BP. AIx was calculated as the difference between the first inflection point (P1) and second systolic peak (P2) on the central BP waveform, and expressed as a percentage of PP. Aortic pulse wave timing (Tr; a surrogate of aortic PWV) was estimated by the SphygmoCor software as the time between the foot of the pressure wave and the first inflection point.

### **A1.3 Results**

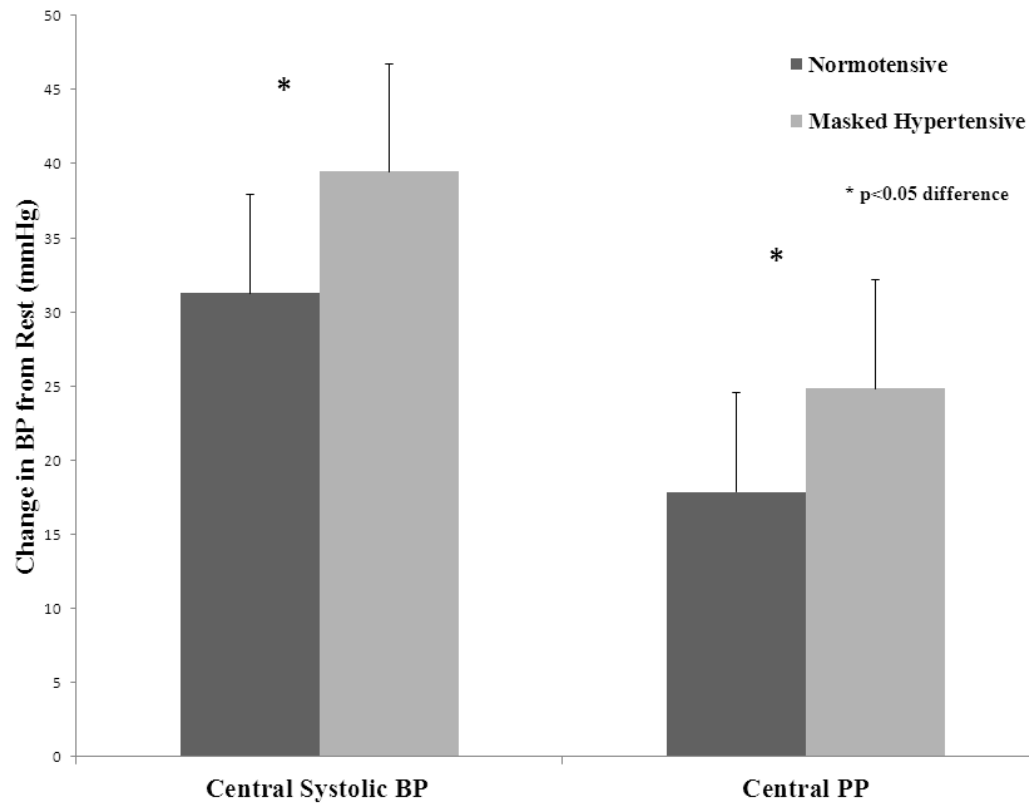
**Pulse wave analysis and the delineation of MH.** Following correction for resting brachial systolic BP, MH subjects had significantly higher central systolic BP, with greater changes from resting conditions (Table A.1 and Figure A.1). The difference in exercise central PP between normotensive's with an HRE and those with MH was of borderline significance. AIx and Tr were not different between groups, either at rest or during exercise. None of the pulse waveform variables, including central systolic BP, central PP, AIx and Tr were significantly different between groups at rest ( $P > 0.05$ ).

**Table A1.1** Central haemodynamic differences between normotensives with an HRE and those with MH.

Variable	Condition	Normotensive with HRE (n=33)	Masked Hypertension (n=42)	P Value	ANCOVA P Value <sup>+</sup>
Central systolic BP (mmHg)	Rest	110(8)	114(8)	.013	.496
	Exercise	141(12)	154(17)	<.001	.019
Central pulse pressure (mmHg)	Rest	37(7)	39(8)	.468	.311
	Exercise	55(11)	64(14)	.006	.051
AIx (%)	Rest	24(13)	20(11)	.115	.305
	Exercise	15(8)	11(10)	.107	.188
Tr (ms)	Rest	146(11)	149(16)	.356	.159
	Exercise	127(10)	128(9)	.856	.800

Data are mean  $\pm$  SD. AIx, augmentation index percentage; Tr, Aortic pulse timing;

<sup>+</sup>ANCOVA corrected for supine resting brachial systolic BP.



**Figure A1.1**

Change in central systolic BP and central PP from rest to exercise for the study population (n=75). Values are significantly different between normotensive's with an HRE and those with MH, (\*P<0.05). Error bars are standard error of the mean.

#### **A1.4 Conclusion**

Central systolic BP, derived non-invasively via pulse waveform analysis, is significantly elevated in individuals with MH and an HRE. Given that central BP is an independent predictor of cardiovascular events and mortality, measurement of central BP during exercise may provide additional clinically relevant information to the diagnosis and treatment of BP abnormalities such as MH.